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Review Article

The extended scope of neuroimaging and prospects in brain atrophy mitigation: A systematic review

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ABSTRACT

Brain atrophy is a condition associated with a reduction of brain volume. It is a common manifestation of aging even though it occurs in some childhood conditions and carried forward to pre-senile middle age.

There are several causes of brain atrophy resulting in different patterns of brain volume loss which spans from focal, global, central, cortical, and hemiatrophy. These conditions are commonly associated with other neurodegenerative changes that lead to different dysfunctions.

Neuroimaging is critical for the diagnosis, evaluation of lesions and quantification of the atrophy. However, radiological quantification of brain volume is done by both automated and manual methods to study brains basing a wide variation of cranial sizes and shapes. A multidisciplinary approach is the future of brain atrophy management. An extended scope of knowledge beyond image interpretation is inevitable.

1. Introduction

Brain atrophy is featured by a reduction in brain volume. The condition is encountered mostly in advanced age but also occurs in some childhood conditions and is then carried forward to pre-senile middle age [1].

There are several conditions reported to induce or accelerate brain atrophy. Some are reversible and some are not [2].

Brain atrophy does not always occur in isolation; paradoxically some other neurodegenerative conditions such as leukoariosis, stroke and perivascular spaces [3] are known to accompany brain atrophy. CADASIL syndrome exemplifies such a complex presentation of neurodegenerative changes [4].

A wide range of clinical manifestations of brain atrophy are recognized and spans from neurocognitive dysfunction, sensory, and motor disorders.

Management of brain atrophy is anchored in a multidisciplinary approach by including clinicians, neuro-radiologists, nutritionists, physiotherapist and policy makers to mention a few; nevertheless neuroimaging plays a vital role in diagnosis, presentation, grading and evaluation of brain atrophy.

In this review, we have discussed the dynamic nature of brain atrophy, its causes, clinical manifestation, serious effects, neuroimaging findings, functional brain mapping and future prospects of brain atrophy management with the broad aim of showing the multidisciplinary contributions needed to study and manage brain atrophy.

2. Materials and methods

2.1. Study design and inclusion criteria

This systematic review was conducted using a meta-narrative approach by highlighting and contrasting ways in which researchers studied brain atrophy and its management using RAMESES publication standards. Articles were included in this review if they met the following inclusion criteria (i) original articles published from February 1971 to May 2020, (ii) cross sectional or cohort studies in English language, (iii) topic with contents related to brain atrophy by causes, findings, management and preventive strategies. Articles in the form of (i) letter to editor (ii) book reviews and (iii) commentary were excluded.

2.2. Search strategies and selection of articles

Published articles from Google-scholar were retrieved and reviewed from February 1971 to May 2020 using key words “Brain Atrophy, Neuro-Imaging, Brain volume, Brain mapping and neurodegenerative changes”. Two independent reviewers screened tittles and abstracts of

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different publications according to the eligibility criteria. A total of 203 papers related to the presented key words were included in this article.

3. Epidemiology of brain atrophy

Brain atrophy is commonly observed in elderly due to aging process; the condition is also known as senile degeneration. However these conditions are occasionally observed in the pediatric age group and carry forward the small volume of brain to middle age, though some atrophic changes may be reversed in childhood [5]. There is scanty information about prevalence of brain atrophy in the general population. Brain atrophy seems to present in wide dynamic ranges of conditions predominantly observed in elderly patients. An example is the prevalence of brain atrophy in liver cirrhosis patients. It has been reported that patients of alcoholic and non-alcoholic cirrhosis have 87.5% and 50% prevalence of brain atrophy respectively [6].

The varying prevalence of brain atrophy is due to age dependent factors [7]. Since brain atrophy may also occur in normal healthy elderly due to aging process, its prevalence may be over estimated by including the normal course of aging [8]. In the normal aging, brain atrophy tends to be accelerated by the presence of other risk factors such as high blood pressure [9], cardiac disease [10], diabetes mellitus [11], smoking practice [12], and regular alcohol intake [13]. Among all these risk factors Glycated hemoglobin A (HbA_{1c}) was noted to be the most significant risk factor for accelerating of brain atrophy [2].

4. The serious effects of brain atrophy in human

There are various clinical features and manifestations of brain atrophy, but the most serious effects of brain atrophy which causes global alarm include poor levels of intelligence especially in growing children [14]. Loss of memory is not uncommon among elderly people [15]. A significant tendency for acute confusional state has been reported in elderly patients with brain atrophy [16]. Loss of functional recovery as an outcome of brain atrophy post infarct [17] which may also lead to death [18] due to poor functioning of the brain [19]. These effects may lead to severe impacts on workforce, authenticity of decisions, and economical disturbance from individual to global level.

5. Types of brain atrophy

Brain atrophy can be classified into various categories. The global or focal atrophy category which depends on the span of brain area involvement [20]. It can also be further classified according to the zonal distribution of volume loss into Central and Cortical Atrophy. Potential areas for examination of brain atrophy in comparison to normal brain are shown in Fig. 1.

5.1. Global type of brain atrophy

The global type is a diffuse form of brain volume loss involving almost all lobes [22]. It tends to be uniform and spans over the whole brain. Among other causes, traumatic brain injury has been reported to induce wide spread degenerative change of the whole brain [23]. Similarly whole brain atrophy may occur in other conditions, although may behave differently in regional distribution. Various processes including infections such as West Nile virus [24], diffuse axonal injury [25], metabolic dysfunctions [26] and malnutrition [27] are among conditions that may be associated with global brain atrophy.

5.2. Regional or focal type of brain atrophy

This has brain volume loss limited in part of brain lobe or some lobes and may not necessarily be symmetrical. Amyotrophic lateral sclerosis (ALS) is among conditions which may cause the regional type of brain atrophy and more commonly involves fronto-temporal lobes

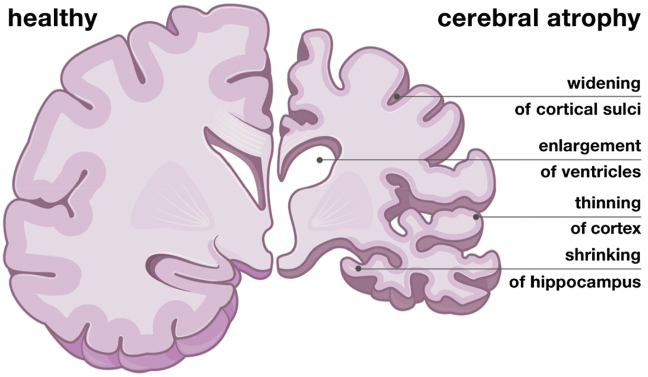

Fig. 1. Areas of interest in observing loss of brain volume. Gross features of unilateral cerebral atrophy following traumatic brain injury. Compared to the healthy right brain hemisphere, the atrophied left brain hemisphere following trauma exhibits widening of the cortical sulci, a gradual enlargement of the ventricles, a cortical thinning, and a shrinking of the hippocampus in the left side [21].

[28]. While Alzheimer's disease (AD) has higher rates of whole brain volume loss, Fronto-Temporal Dementia (FTD) mainly shows higher rates of brain atrophy in anterior and temporal parts of the brain. In addition AD and FTD have their annual brain volume loss rated at 2.4% and 3.2% respectively [29].

5.3. Central type of brain atrophy

It is a pattern which dominates the central region of brain. In this category the white matter volume loss is more than the gray matter in brain cortex. The ventricular size is very important in establishing prognostic marker of some conditions like multiple sclerosis. In this and other white matter conditions, central atrophy of the brain is more important in patient monitoring than global atrophy [30]. The centricity of pathology explains why loss of white matter volume is more in this category and hence it is measured by increasing ventricular fraction [31].

5.4. Cortical type of brain atrophy

This form of brain atrophy involves; the volume loss in the peripheral parts of the brain such that there is loss of more gray matter than white matter. Diabetes type 2 is one of many other causes associated with cortical brain atrophy [32]. The use of clozapine drug in Schizophrenia patients has been associated with cortical thinning in pre-frontal cortex of brain [33]. The periphery nature of mechanism of tissues injury is the reason why white matter changes are uncommon in cortical atrophy.

In some scenarios, cortical atrophy may also occur in cases of multiple sclerosis, however, the distribution is not diffuse, rather, it tends to be in a non-random manner [34]. Its distribution depends on the pattern of the white matter changes, therefore, it has closer association with clinical findings [34]. Regional selective and cortical atrophy has been also reported in diffuse axonal injury [35].

5.5. Brain hemiatrophy

This is another type of brain volume loss and usually described in accordance with hemispheric laterality by involving one of the brain hemispheres in totality. Rasmussen encephalitis [36], Dyke-Davidoff Masson Syndrome [37], Parry-Romberg syndrome [38] is among the frequent culprits responsible for hemiatrophy of brain. The other conditions are thought to be the results of insult during fetal or early neonatal life [39]. The neurocutaneous conditions also known as phakomatoses including tuberous sclerosis and Sturge Weber syndrome are

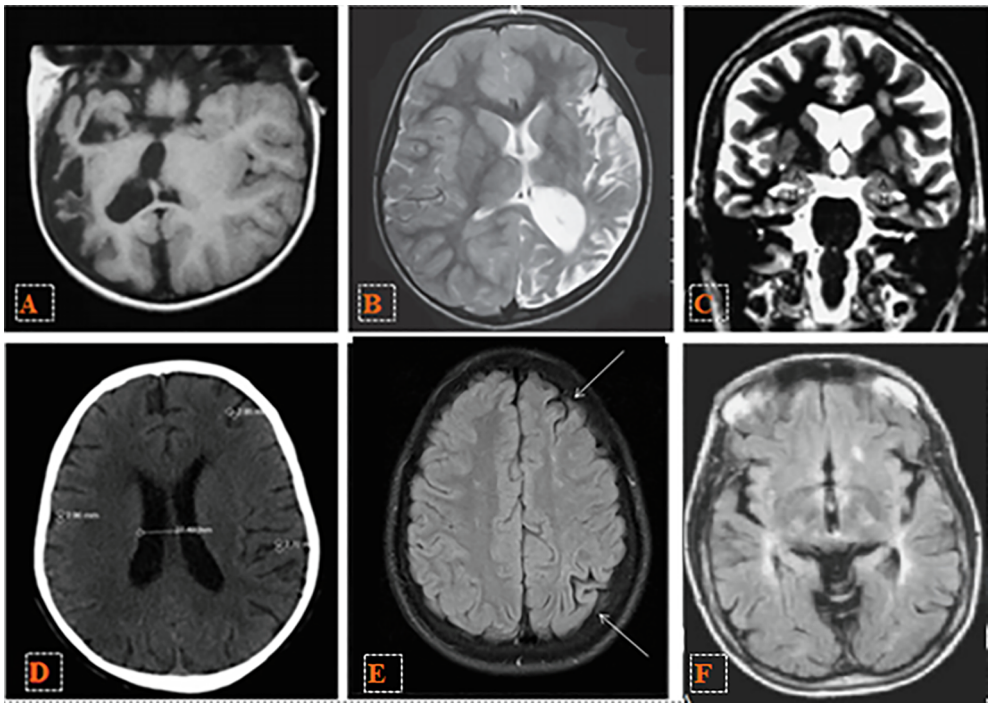

Fig. 2. Types of brain atrophy. A:Right brain hemiatrophy on MRI [37], B:Left brain hemiatrophy in nine years girl MRI image [41] C:Global brain atrophy in T2-coronal MRI showing involvement of hippocampus and amygdala [42] D:Cortical brain atrophy evidenced by widening of sulci > 2.5 mm in a pediatric patient on CT image [43], E:Focal or regional atrophy in the left frontal and parietal occipital lobes on MRI [44] F:Central type of brain atrophy, well measured in multiple sclerosis patient showing enlarged 3rd ventricle per age [45].

commonly associated with hemiatrophy of brain [40]. Varying anatomical appearance of categories of brain atrophy are shown in Fig. 2.

6. Causes of brain atrophy

Brain volume loss in human is caused by several factors. For the purpose of this review these causative factors are examined and organized into major categories.

6.1. Age related brain atrophy

The condition is also known as senile brain atrophy. It is contrasted from pediatric brain atrophy which usually must have a co-existing pathology such as meningitis [46] and traumatic brain injury [47]. In the normal course of life the brain grows by increasing in volume for the first two years with grey matter growing faster than white matter [48]. Brain attains its optimal volume at the fourth decade of human life and this is followed by a slow decrease in volume toward senility [49].

Studies show that from one to ten years of age there is a rapid increase in gray matter volume which is then followed by progressive decrease in volume while white matter has its maturation peak in middle age [50]. Sex differentiation of brain volume specifically the gray matter and white matter volume is influenced by the gonadal hormones from intrauterine and in later life [51]. While men have larger white matter volume, women have larger gray matter volume [52].

Aging is a dynamic process at different stages of life. Age related brain changes include atrophy, white matter disease, cerebral micro bleeds [53].

Trajectories of brain atrophy from the age of 45 years showed nonlinear decrease in brain volume according to the Rotterdam study by [54]. Trajectories of the different volumetric, microstructural, and focal markers showed a nonlinear curve. Accelerated change was evidenced with age advancement.

When specific gray and white matters of brain are considered separately, gray matter changes in volume differently from the white matter where as an average of 2.4 ml of gray matter volume is reduced per year and is associated with a paradoxical increase in CSF volume of 2.5 ml per year. The white matter shows no significant volume loss, though the seemingly loss in volume is observed preferentially in the anterior part of corpus callosum as seen through optimized voxel based morphometry (VBM) in brain studies of the elderly [55].

Shaw et al, 2016 conducted an age specific study for healthy individual between the ages of 60 and 66 years with an objective of studying the patterns of cortical thinning of the brain using MRI. The study revealed an average volume loss of cortex by −0.3% every year except in areas which atrophies later in life such primary sensory cortex. In this study it was noted that men exhibited more extensive cortical thinning than women [56].

6.2. Infections of central the nervous system (CNS)

Inflammatory reactions in the brain have been associated with damage of brain cells and hence causing loss of volume. Retroviral infection is a common condition causing brain atrophy. When the disease is progressed to HIV encephalopathy; it commonly presents with brain atrophy [57]. A study by [58] observed a specific pattern of brain atrophy in HIV encephalopathy; the pattern is commonly a central atrophy that primarily affects the subcortical white matter or the basal ganglia [58].

Meningitis has also been associated with events of brain atrophy [59]. In Sub-Saharan Africa HIV related cryptococcal meningoencephalitis is the most common type of meningitis. This condition in initial stages has very few radiological findings even on MRI [60]. However, one of the findings is the presence of prominent Virchow-Robins spaces or pseudocysts [61]. Others include enhancing nodules and hydrocephalus [62].

Cerebral malaria is also an infective cause of brain atrophy [63]. Studies have shown that among many other features children with cerebral malaria suffered loss of brain volume [64].

6.3. Nutritional deficiency as cause of brain atrophy

The deficiency of Thiamine (vitamin B_1) has been associated with brain atrophy since it plays an important role as a co-factor for several enzymes in the metabolism of neurons [65].

Similar to Thiamine, Cobalamine has also been associated with

brain atrophy when it is deficient in human [66]. MRI scans proved a reversal of atrophy after B_{12} therapy [67].

Cobalamine, Folate, and Thiamine are all known to be water soluble vitamins; hence, they have an unstable state in human blood. Therefore, future investigation should rely more on studying the timing of these vitamins deficiencies [68].

Protein-energy malnutrition is another condition that is related to poor development of brain volume and brain atrophy as proteins such as DYRKIA are important structural component of nerve fibers [69]. Hence protein-energy malnutrition has serious effects on the central nervous system including changes in brain volume [27] and a decline in mental performance [70].

6.4. Metabolic and endocrine causes

Hormones work closely with nutritients on brain growth and function. An Insulin Like Growth factor-1 (IGF-1), is a neurotrophic hormone that plays important function in CNS development and maturation [71]. It is important in adaptive changes of CNS in meeting functional demand, a process known as neuroplasticity [72].

Brain atrophy resulting from cellular damage may be the caused by an inborn error of metabolism [73]. A distinct pattern of changes in pediatric brains with biotinidase deficiency have been shown on CT and MRI [74]. Other metabolic studies have shown diffuse changes of the white matter followed by progressive loss of brain volume [75]. Biochemical tests for enzymes are necessary.

Glutaric aciduria type 1 (GA1) is a rare metabolic disorder caused by a deficiency of glutaryl-CoA dehydrogenase enzyme. In this condition the body is unable to completely break down amino acids lysine, hydroxylysine and tryptophan leading to excessive intermediate products with potential to cause damage of the brain tissues in early age [76]. GA1 may mimic a non accidental injury on imaging including some hematoma and retinal hemorrhages [77]. Fronto-temporal type of atrophy is another significant finding [78]. It is treated by dietary restriction of lysine and tryptophan, supplemented with L-carnitine and riboflavin amino acids. The condition is a reversible cause of brain atrophy when well managed [76].

Many pediatric conditions in developing countries are hidden in the back ground of inborn error of metabolism [79]. Metabolic causes are not only limited to children but they are far reaching to all ages. A study that compared the diabetic and non-diabetic elderly noted significant difference in total brain volume; the study showed that the hipocampal volume of the quantitative MRI images of the two groups differ such that the subjects with longer duration of diabetes and elevated 2-h PG level showed much reduction in brain volume with predominance in the hippocampi [80]. Therefore, duration of illness can be the risk factor for brain atrophy in diabetics.

Brain atrophy has continually been observed in other endocrine conditions like Cushing disease due to pituitary adenoma which triggers over secretion of cortisol a steroid hormone from adrenal gland. In the study by Bhurkardit et al, it was shown that patients with Cushing disease for a minimum of 24 months have significant grey matter volume loss in cerebellum and hippocampi [81]. Hence, Cushing syndrome is an important endocrine cause of brain atrophy.

6.5. Traumatic causes of atrophy

Trauma is among the common mechanisms of brain injury leading to brain atrophy. Traumatic brain injury causes structural and functional changes on neurons and some of these are long term changes. When comparing the brains of patients with traumatic head injury in relation to healthy individuals of the same edge, the study by Cole et al revealed significant loss of brain volume in traumatic cases that was almost similar to that of older individuals [21]. Diffuse axonal injury commonly results into global atrophy that may mimic age degeneration [1]. Hence, it was concluded that traumatic brain injury accelerates aging.

Chronic neurodegenerative changes due to repeated concussions (mild traumatic brain injury) have been noted among boxers and individuals playing contact sports [82]. The mechanism is thought to be caused by activation of the microglial cells and astroglials in causing traumatic brain inflammation [82]. A study by [83] also suggested that the injury to brain cells, causes attraction of the macrophages or microglia which attempt to consume the damaged cells but in so doing they also unselectively engulf the health cells leading to progressive loss of brain volume [83]. In previous studies it was also observed that brain atrophy occurs at an average of 11 months after head injury. Trauma that results into loss of consciousness (LOC) leads to severe form of atrophy [84].

A review paper published by Bigler, 2013 cited the work done by Maxiwel*et al* using postmortem study where it was shown that approximately 112 cc of brain volume is lost in relatively young patients as a result of brain atrophy caused by traumatic brain injury [85]. Head injury remains to be an important cause of brain atrophy [86].

Head CT scans performed before surgery and at early and late postoperative periods, comparatively revealed extreme bilateral cortical atrophy in a patient who had a severe head injury [87].

6.6. Drug induced brain atrophy

Antipsychotics and anti-epileptics are among drugs linked with causation of brain atrophy. Ho et al., 2011 published a relationship between the level of antipsychotic drugs taken over the period of time and the amount of brain volume loss as measured by a series of MRI scans [88]. Other studies shows that anticancer drugs including thiotepa have serious effects in causing brain atrophy in children [89].

Chemotherapy is a lifesaving mode of treatment in various cancers including breast cancer. However, the side effects of these drugs are borderless and may tend to damage sensitive cells of other organs. When the CNS involved it may lead into brain atrophy and results into serious cognitive decline [90]. When administered in high dose, the oncological treatment of high grade tumors such as glioblastoma may cause severe side effects including brain atrophy [91].

6.7. Radiation induced brain atrophy

Radiations with ionizing potential have remarkable effect in causing brain atrophy especially when their high energy beams are directed toward the head and neck region [92]. Radiation may come from the natural sources like cosmic rays but most remarkable is radiation from manmade sources such as diagnostic X-ray and Radiation therapy. There is direct correlation between ionizing radiation with formation of neurodegenerative diseases. The sequence of events starts from DNA damage, hypoxia, mitochondrial dysfunction, neuronal injury, followed by reduction in neurogenesis and finally neurodegenerative disorder [93].

The effects of radiation on brain tissues are dependent on the fractionated dose applied to irradiate the brain. The cortical thinning of the brain is increased when the radiation dose is higher [94]. Apart from the issue of reducing brain volume, ionizing radiation also reduces brain tissue perfusion and it is dose dependent even if proton radiation is used [95].

The increase in human activities and technology has led to more exposures of ionizing radiation. This includes natural ionizing radiation such as cosmic rays from the aerospace industry [96]. Atrophy and mental changes are recognized effects of high altitude occupations [97].

Medical staffs working in radiology and interventional cardiology units where x-ray fluoroscopic examinations are done have not been exempted from radiation issues despite data deficiency. The staffs in interventional cardiology may get a life span cumulative radiation dose up to 500 miliSievert (mSV) while the permissible dose for staffs' life span is 200 mSV [98]. A minimum radiation dose sufficient to cause

significant tissue damage including brain atrophy is 0.5 Gray which is also equal to 500 mSV [99].

6.8. Increased intracranial pressure

Hydrocephalus is another lesser known cause of brain atrophy; it is among congenital anomalies in children but may also occur as an acquired case in later life. If pressure is not decompressed, permanent atrophy may be the end result, starting with white matter toward cortex, according to Tully *et al.* (2016) [100]. When left untreated, hydrocephalus causes brain atrophy and it may also be fatal [101].

6.9. Perinatal and birth injury induced atrophy

Hypoxic ischemic encephalopathy also known as birth asphyxia is among the causes of neonatal encephalopathy. Other causes of encephalopathy includes infections and metabolic causes [102]. During birth asphyxia the brain suffers low oxygen tension and among the earliest changes is brain edema. When oxygen depletion is allowed for long time it will results the destruction of brain tissues and consequent loss of volume [103]. Trans-cranial ultrasound is a powerful primary non-ionizing radiation tool for the detection of acute and then chronic changes of birth asphyxia prior to the use of a CT scan and MRI [104]. Survivors of birth asphyxia may have delayed developmental mile stones [105].

The delayed motor milestones of development is known as Cerebral palsy and frequently results from traumatic birth injury due to obstructed or long labor [106]. The mechanically damaged part of the brain may result into focal atrophy [107]. However these kind of injuries seem to elude diagnostic imaging in early stage until later in life when attention is made on the motor manifestation of Cerebral palsy [108]. Studies involving Cerebral palsy children show that grey matter is affected more than white matter [109].

6.10. Neurodegenerative diseases causing brain atrophy

Alzheimer's disease is an important consideration in this category. It is a condition associated with loss of memory. Its pathogenesis is not clear but it is thought to result from multiple interactions of immunological mechanisms [110]. Despite unending debate about the pathogenesis, worldwide evidence supports the concept of an imbalance between the production and clearance of Aβ42 and other related Aβ peptides as initiating factors in Alzheimer's disease development [111]. Medial temporal lobe atrophy is a common presentation of Alzheimer's disease a finding which can be depicted by CT scan or FGD-PET [112].

Multiple sclerosis is a genetic and familial white matter inflammatory demyelinating disease [113]. The condition occurs in phases and the most important outcome of multiple sclerosis is brain atrophy [30]. It was noted and reported that multiple sclerosis causes a rate of $-0.51 \pm 0.27\%$ brain volume loss per year while a healthy individual experiences $-0.27 \pm 0.15\%$ brain volume loss per year [114].

6.11. Other causes of brain atrophy

Autoimmune condition like limbic encephalitis are derived from polychondritis an autoimmune condition affecting cartilages. This rare condition has been found to cause brain atrophy in the temporal lobes with MRI changes in the basal ganglia and hippocampi [115].

While a symmetrical pattern of brain atrophy is the most common, a few conditions have been known to present with a unilateral form of brain atrophy. Dyke Davidoff Masson syndrome is among conditions associated with hemiatrophy of the brain [37]. The condition is thought to originate from Cerebral injury during the perinatal period of brain development [116]. Apart from loss of volume in one hemisphere, the condition is associated with increased skull thickening in ipsilateral side as a compensatory mechanism or exvacuo effect [117].

Tuberous sclerosis is an additional rare multisystem genetic disease that causes non-cancerous tumors or growths. The disease is among the list of phakomatoses. The growth can occur in the skin, kidneys, heart or lungs. In the brain it is common to find cortical tubers or subependyml nodules and brain atrophy. Seizures are the main clinical presentation [118].

Sturge-Weber Syndrome is another phakomatosis or neurocutanous conditions associated with brain atrophy. The cardinal imaging features of this condition include unilateral gyral calcification in the brain, capillary-venous malformation with a high tendency of contrast enhancement and also facial nevi [119]. The pattern of brain atrophy is characteristically hemiatrophy while epilepsy is the most common clinical presentation [120].

The frequency and duration of seizures from Sturge-Weber syndrome have proven to contribute to the severity of cognitive dysfunctions evidenced by low IQ performance [121]. These findings were noted to depend on laterality of the condition. It was found that the effect is more global when the right hemisphere is involved [122].

In another study, with unilateral Sturge-Weber syndrome, it was noted that early onset, repeated seizures and inter-ictalepileptiform abnormal discharges on EEG tend to interfere with process of functional reorganization of brain resulting in poor cognitive functions [123].

Rasmussen Syndrome is also known as chronic focal encephalitis. It is associated with slowly worsening of neurological deficit and commonly found in children. Its imaging finding includes typically brain hermiatrophy with its focal lesion looking like focal cortical dysplasia [124].

Sickle cell encephalopathy is generally rare but not uncommon in some ethnic groups like Nilotic and Bantus communities of Sub-Saharan Africa where the condition with Haemoglobin SS is prevalent [125]. When poorly controlled, the condition causes a range of changes in the brain, spanning from brain atrophy, infarcts, encephalomalacia, and leukoencephalopathy. It must be considered in clinical evaluation of children presenting with brain atrophy [126].

7. Common clinical findings of brain atrophy

When Brain atrophy occurs in severe form or in advanced age it rarely exists in isolation but is frequently associated with white matter changes and/or stroke. Apart from causing other regional specific deficits, these conditions may cause patients to present with cognitive impairment, dementia, urinary or fecal incontinence, gait disturbances, poor executive functions, depression, unilateral loss of power in stroke, and poor learning in children [127].

Neurocognitive function show significant decline when there is brain atrophy or presence of white matter lesions [128]. Excessive alcohol consumption may lead to Korsakoff syndrome and increased neurocognitive decline due to brain atrophy [129].

Visual spatial and perceptual disturbances are common manifestations of posterior cortical atrophy (PCA) however not all patients with PCA have obvious clinical evidence of atrophy [130].

Studies suggest that PCA is a variant of Alzheimer's disease due to its pre-senile onset, location and asymmetrical nature [131].

Mild traumatic brain injury is associated with brain atrophy, however it has been shown that the accompanying loss of consciousness tend to cause a severe form of brain atrophy 11 months after the injury [84]. A predictive marker of anticipated brain atrophy was observed through Biochemical analysis by micro dialysis techniques where it was suggested that persistently elevated Lactate-Pyruvate ratio of > 40 is predictive of brain atrophy at 6 months' post head injury [132]. Another laboratory predictor of brain atrophy development is the high levels of CSF neurofilament heavy chains (NfH) proteins which are known to be biomarkers of axonal loss from brain tissues [133]. Normalized brain volume as studies by MRI is (1.44 L vs 1.33 L, $p < 0.05$)

while normalized grey matter volume (0.77 L vs 0.69 L); hence the presence of high levels of NfH in CSF is an early predictor of brain and spinal cord atrophy [134]

Another clinical manifestation of brain atrophy is infantile tremor syndrome [135]. In this condition children present with unusual tremors.

8. Imaging findings of brain atrophy and associated challenges

The pattern of brain atrophy in some conditions is closely related with causative pathology. There are different patterns of brain atrophy depending to the causes. These patterns can be studies by various imaging techniques including Trans-cranial Ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET).

For age related brain atrophy, changes are seen in both grey and white matter volume loss. While grey matter volume is loss has a linear relation with age, the white matter volume loss is somehow faster and exhibits a quadratic relation with age [136].

When is caused by multiple sclerosis there is a tendency for increased values of Bi-caudate ratio values [137]. Multiple sclerosis is rare condition among Africans [138]. However, for patients with multiple sclerosis a different pattern of brain atrophy has been noted. While the relapsing-remitting type of multiple sclerosis, shows mostly central atrophy, the progressive forms present predominantly with cortical type of atrophy [139].

The ventricular dilatation and widened Sylvian fissures at various degrees are among the common findings of brain atrophy. They have been reported in infants with protein-energy malnutrition [140]. The severity of atrophy is closely related to the duration of the illness [141].

As a general trend ischemic stroke and brain atrophy are commonly seen among elderly patients and closely associated with white matter demyelinative changes also known as leukoariosis. Ursula et al., 2013 observed the severity of leukoaraiosis being 62% in men with average age of 71 years old [142].

Diabetes mellitus is an emerging non communicable disease globally. Studies have shown its strong association with three major changes in the brain. These are cerebral atrophy, stroke and white matter lesions [143]. Del Bene et al., 2015 showed a strong relationship between the presence and severity of leukoariosis and type 2 Diabetes mellitus [144]. Even though the imaging findings may not differ much in each category of brain atrophy, there are varying differentials in each category among pediatrics and adult patients as summarized in Table 1.

Progression of leukoaraiosis relates to cognitive decline, but this association suggests that punctate abnormalities on MRI have a low tendency for progression. Individuals with early confluent changes tend to progress rapidly [127]. The stages of progression of leukoariosis and their clinical picture are recognized as initial, intermediate and terminal stages [145]. The presence of MRI white matter changes are indicative of increased risk for stroke, dementia and mortality [146]. The smaller the lesion, the lower the impairment, but as the lesions become larger there is more functional decline in the cognitive domain which includes executive function, processing speed and memory capacity [145].

The severity of leukoariosis and other white matter changes were revealed by the Fazekas scale which later appeared to have challenges due to different sensitivity between CT and MRI. Another scaling system was designed and presented as the New Rating Scale for Age-Related White Matter Changes applicable to MRI and CT [147]. Some current studies suggest that the Fazekas scale can still be used reliably on CT scan in the absence of MRI [148]. Imaging findings of leukoarisis as per Fazekas classification are summarized in Fig. 3 and Table 2.

When tested with instrumental activity of daily living (IADL), Leukoarisosis and Disability (LADIS) increases with the size of white matter lesions on CT/MRI when classified as mild, moderate, and severe white matter lesions according to the Fazekas scale [158], refer Table2. These testing parameters include global functioning, cognitive function, motor, psychiatric examination and quality of life measures.

Evaluation of brain atrophy is an extensive subject in diagnostic radiology. In age related brain atrophy, the volume changes can be evaluated with a Visual qualitative approach or other quantitative ways. A common visual qualitative method is Global Cortical Atrophy using a scale from 0 to 3. It may be considered at GCA-0, GCA-1, GCA-2 and GCA-3 as mild, moderate and severe atrophy according to the Global Cortical Atrophy-Frontal subscale (GCA-F) [159]. A GCA score-2 is abnormal for a person below 75 years while GCA-3 is always abnormal irrespective of age (knife blading). A similar qualitative method can be used to evaluate the medial temporal lobe atrophy (MTA) with a score from 0 to 3. A unilateral score of at least 2 is abnormal for subjects below 75 years. Paradoxically it takes a bilateral score of at least 2 to declare abnormality for subjects older than 75 years of age. A score of at least 3 is always pathological and indicates MTA [159].

While the visual qualitative methods are prone to subjectivity, objective quantitative methods of brain atrophy are also available in assessing brain volume loss. The methods are grouped into two categories:

(i) *Manual mathematical evaluation* of brain atrophy using linear measurements of ventricle such as One-dimension (1-D) through the body of lateral ventricle (> 30 mm) and at least two sulci (> 2.5 mm) are the indicators of brain atrophy according to the Dunham protocol [160]. The use of ratio such as the Evans index using the measure of the line through the anterior horns of the lateral ventricle divided by the widest diameter of the inner table of skull is used in evaluation of both hydrocephalus and brain atrophy; the normal value is < 0.3 [161].

(ii) *Automated methods;* are the software based methods that are used within cross sectional imaging machines such as CT and MRI. The methods include software segmentation techniques that produce the actual brain volume and CSF in ventricles and cisterns [162]. Automatic segmentation methods go as far as estimating total volume of white matter demyelinated volume using Brain Intensity Abnormality Classification Algorithm (BIANCA). BIANCA is a supervised automatic method which uses the k-nearest neighbor (k-NN algorithm), with flexible features of MRI [163]. Most automated methods consider variation in cranial size to measure to perform brain volume studies [164]

The diagnostic aspect and functional study of brain atrophy is not limited to cross sectional imaging but it is far reaching as far as brain mapping and electrophysiological studies. The history of brain functional mapping started in eighties using short acting radiotracers on Positron emission tomography (PET). One part of the brain responds differently from another part during activation [165]. A radioisotope oxygen in water is among the common radiotracers utilized by PET in doing functional mapping to study the brain tissues perfusion expressed as regional cerebral blood flow (rCBF) [166].

An extensive merging of disciplines is required to give a full understanding of brain functions and how it supports mental activities. It includes an understanding of neurophysiology, cell biology, and genetics of the imaging signals of human brain [167].

The mapping techniques are grouped in two categories namely haemodynamic (fMRI, PET, SPECT (single photon emission computed tomography) and Near Infrared Spectroscopy) and Electrophysiological techniques (qEEG, MEG and Trans-cranial Magnetic Stimulation) [168].

Currently brain mapping is achieved through collection of the multivariate data through high resolution neuroimaging and multi electrode electrophysiological recording which include PET, MRI, qEEG and MEG [169].

While MRI provides high spatial resolution of functional brain mapping, EEG and MEG have good temporal resolution and therefore methods complement each other by maximizing the resolution of each method [170].

In Biofeedback, the mapping devices like EEG can inversely be utilized to provide feedback to the brain and as a result trains the affected parts of the brain to improve their functional status by delivering

Table 1
categorical distribution of the brain atrophy determinants and their diagnostic imaging clues.

Atrophy category	Anatomical and imaging clues	Possible causes of brain atrophy	
		Pediatric	Adults
Global atrophy	- Involvement of whole brain - Widened sulci in all lobes [149] - Dilated ventricles	- CNS Infection - Malnutrition - Metabolic dysfunction [26] - Hypoxic ischemic encephalopathy [102] - Sickle cell disease [1] - Chemotherapy [89] - Miscellaneous	- Age related - CNS Infection - Chronic illness - Chronic alcoholism [150] - Post diffuse axonal injury - Metabolic dysfunction eg-hepatic failure, diabetes mellitus [143]. - Chemotherapy - Miscellaneous
Cortical atrophy	- Involvement of whole brain - Widened sulci and in all lobes - Ventricles may be normal [149]. - Reduced grey matter volume by segmentation [149]	- CNS Infection - Malnutrition - Metabolic dysfunction - Hypoxic ischemic encephalopathy - Miscellaneous	- Age related - CNS Infection - Chronic illness - Neurotoxic chemotherapy [91] - Post diffuse axonal injury [25] - Metabolic dysfunction - Miscellaneous
Central atrophy	- Involvement of whole brain centrally - Normal sulci and in all lobes - Dilated ventricles [151]. - Increased bi-caudate ratio - Reduced white matter volume by segmentation [145]	- Multiple sclerosis [30] - Metabolic dysfunction - Hypoxic ischemic - Hydrocephalus [152] - Miscellaneous	- Leukoarisis of elderly - White matter disease eg-Progressive multifocal leukoencephalopathy [153] - Metabolic dysfunction - Miscellaneous
Focal atrophy	- Localized or lobar involvement - Sulci may focally be widened - Asymmetrical ventricular dilatation	- Trauma - Space occupying lesion [154]. - Alzheimer's disease - Amyotrophic lateral sclerosis - Frontal temporal dementia - Radiotherapy - Miscellaneous	- Trauma - Space occupying lesion eg abscess or tumor. - Radiotherapy [92] - Miscellaneous
Hemiatrophy	- Hemispheric involvement - Hemispheric sulcal widening - Hemispheric ventricular dilatation - Hemispheric reduction of grey or white matter volume	- Rasmussen encephalitis - Dyke-Davidoff Mason's syndrome - Tuberous sclerosis - Sturge-Weber syndrome - Parry-Romberg syndrome [38] - Trauma [155] - Miscellaneous	- Trauma - Hemispheric ischemia - Pediatric syndromic caused carried to adulthood. - Miscellaneous

current density within a brain volume using (Low Resolution Electromagnetic Tomography (LORETA) modeling. Possible application of neurofeedback includes treatment of epileptic foci and rehabilitation of a specific part of the brain affected by traumatic brain injury [171].

In another study an advanced application of MRI tractography was used to determine whether after NFT there is a change or increase in Grey matter volume in the region of interest. Participants were trained to enhance the amplitude of their β1 waves at F4 and P4. It was found that after neurofeedback training (NFT) there was increased fractional anisotropy measured in white matter pathways and Grey Matter in specific areas involved in the training [172].

In general, there is little written about the effects of brain atrophy on brain mapping. A fraction of information has been documented about neurodegenerative condition. Amygdallo-hippocampal atrophy is a focal brain volume loss in part of the temporal lobe. One study showed an increase in alpha2 and alpha3 power of EEQ findings, but when the Amygdala and hippocampal are studied individually a high Theta/Gamma ratio is specific to amygdala atrophy and alpha3/alpha2 ratio points toward hippocampal atrophy [173].

9. The future perspective of brain atrophy management

Since there are some forms of atrophy that cannot be treated currently, then the future of brain atrophy management relies on reversibility mechanisms and preventive approaches.

9.1. Reversibility of brain atrophy

Reversibility of brain atrophy is one of the most important clinical goals for sustaining good health. It seems to be dependent on the causative agent and the nature of tissue injury.

Studies have shown good outcome in nutritional related brain atrophy especially that related to protein-energy and vitamin related malnutrition. The use of vitamin B12 has shown significant improvement from the loss of brain volume especially in children [135]. In children with genetic metabolism error, a supplement of metabolite like biotin has shown improvement in brain volume recovery [74]. Tremendous improvement of cognitive function and brain volume is anticipated for children with kwashiorkor when is managed in a timely manner [70].

Treatment of the offending cause is important. Progressive HIV encephalopathy (PHIVE) presents with several brain changes including atrophy. These changes have shown reversal evidence when HAART has been consistently utilized especially in children with a growing brain. PHIVE may therefore considered be a reversible cause of brain atrophy [174].

For the patient whose brain atrophy has its root from Cushing syndrome due to pituitary adenoma or other hypersecretion cause of glococorticoid hormone, improvement in brain volume has been noted after treatment of the cause [175].

A study by Tsai et al., 2017 suggested that pharmaceutical composition for treating brain atrophy can work by inhibiting excitatory synapses in dementia and therefore improve memory [176].

Neurofeedback can also be done using functional MRI so that participants can train to modulate activation levels to specific parts of their brain and hence regulate emotions by focusing on positive mood [177]. Since the 1960s EEG neurofeedback was used to manage some mental illnesses with controversial effectiveness. Kluetsch et al showed EEG

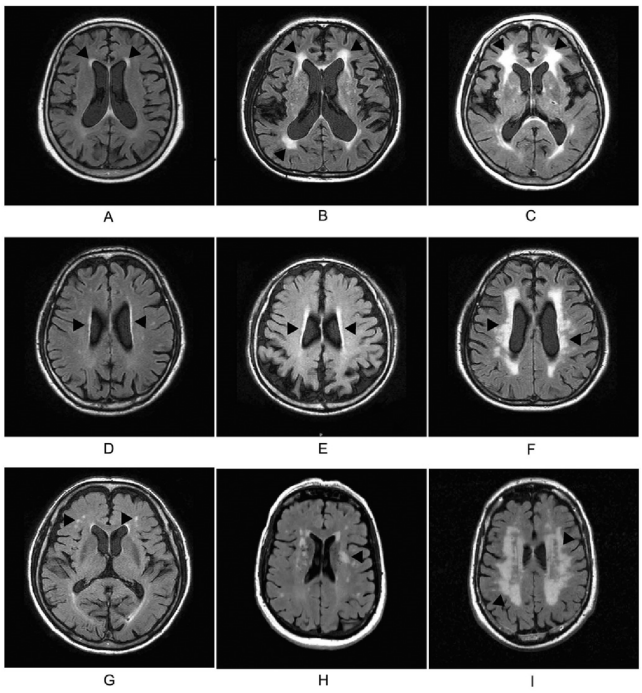

Fig. 3. Stages of white matter degenerative changes. Forms of white matter lesions (WML); small caps (A), large caps (B), extending caps (C), thin lining (D), smooth halo (E), irregular periventricular WML (F), punctuate deep WML (G), deep WML beginning confluence (H), confluent deep WML (I) [156].

rebound after neurofeedback treatment in a case of Post-Traumatic Stress Disorder (PTST) [178]. Currently neurofeedback methods using advanced neuroimaging show a promising future in self-regulating brain conditions [179]. There are multitudes of brain atrophy determinants spanning from reversible to irreversible form. The most commonly occurring determinants, their clinical manifestations and their possible managements are summarized in Table 3.

9.2. Prevention of brain atrophy

9.2.1. Primary preventive measures

In this strategy, the goal is to prevent the population from getting exposure to the manageable risk factors.

Among many factors, the most alarming ones includes improvement of neonatal care for the vulnerable. When maternal health services are improved, timely management will reduce incidences of birth asphyxia and eventually pediatric brain atrophy [103].

Laws and regulations for road safety is another primary preventive strategy to reduce head injuries due to traffic accidents [189]. Traumatic brain injury is a well-known causative factor for brain atrophy [190].

Advancement in nanotechnology sheds light on alternative ways to deliver optimum drug concentration at a specific lesion with minimum effects to other innocent organs. This includes fabricated biodegradable multi agent nanofibrous membranes (drug loaded nanofibrous membranes) using electrospinning process to provide sequential and sustained release of the chemotherapeutic agents [191]. These kinds of technologies will reduce exposing the brain to highly cytotoxic anticancer drugs hence less incidents of brain atrophy.

9.2.2. Secondary preventive measures

In this category, the strategy aims to mitigate further damages from the already exposed population, including recovery of some functions. Anti-macrophage therapy is one of the future possibilities in mitigating brain atrophy induced by traumatic brain injury. It has been highlighted in many publications regarding neurodegenerative changes that are initiated by inflammatory reaction through macrophages. It is suggested that any therapeutic process that inhibits macrophage (anti-macrophage) might be effective in preventing these cells phagocytosing other innocent neurons after traumatic brain injury [83]. It is however noted that most anti-inflammatory therapies have been poorly effective in achieving this preventive role of neurodegeneration, hence there is a need to extend efforts to additional clues that have been enriched by advancement in neuro-imaging; this include the idea of inflammasomes, mechanisms of microglial polarization, and glymphatic clearance. These concepts could create a window for novel therapeutic target [192].

Sterm cell neuro-regeneration is a genetic engineering advancement that has a promising future is leaning on. Many technical mechanisms are under investigation including adipose derived stem cells which have shown potential for inhibiting cerebral infarction by altering macrophage function kinetics [193].

Stem cells from different individuals may work differently. A study done in mice using human mesenchymal stem cells (hMSC) have shown that the age of the donor seems to affect stroke lesions, so the younger the donor, the more effective the stem cells [194]. Ischemic stroke or cerebral infarct is among the most common causes of focal or regional type of brain atrophy [195].

Citicoline is another agent thought to be of future usefulness in mitigating progression to brain atrophy in children subjected to birth asphyxia. The dug has shown neuroprotective role in animal experiment when given in a dose 300 mg/kg through pareteral administration [196]. It is therefore anticipated that this pharmaceutical agent may have future significance for human in events of hypoxic ischemic encephalopathy associated to birth injury.

Another neuroprotective mechanism of preserving brain volume include activation of the amyloid precursor protein though the use of minocycline. Apart from the thought role of neuroplasticity and synapsis regulation the protein is reported to be neuroprotective [197]. Therefore, multi target approach is the future of brain atrophy mitigation.

10. Discussion

Brain atrophy is a vastly dynamic process; moreover, there is no generalized information about the community magnitude of the problem apart from publications addressing brain atrophy in isolated conditions such as the prevalence of brain atrophy among patients with

Table 2
Fazekas scale of white matter demyelination.

Fazekas scale	Descriptions	Reference	Image example	Reference
1	MILD -Punctate lesions not > 9 mm	[157]	A, D, G	[156]
2	MODERATE -Early confluent lesions between 10 and 20 mm -no more than connecting bridges	[157]	B, E, H	[156]
3	SEVERE -Single or confluent lesions > 20 mm	[157]	C, F, I	[156]

Table 3
Brain atrophy types and their clinical implication.

Brain atrophy type	Common differential determinants	Clinical presentation	Current treatment options
Global brain atrophy [29]	Advanced form degenerative atrophy Infection such as encephalitis Malnutrition [27]	Headache [180] Tremors [135] Loss of memory [15] Convulsions Dizziness [1] Vertigo [181]	-Treatment of offending cause (eg HIV) -Mainly supportive -Nutritional supplements involving Vitamin B1, B12 and proteins [67]
Focal brain atrophy [182,182]	Head trauma Localized space occupying lesion Stroke or ischemia	Headache Convulsions [183] One side body weakness	-Treatment of offending cause -Mainly supportive involving anticonvulsant drugs. -Neurofeedback stimulation
Central brain atrophy [30]	Previous hydrocephalus Multiple sclerosis Malnutrition	Headache Tremors	-Treatment of offending cause (eg hydrocephalus) -Mainly supportive -Nutritional supplements involving Vitamin B1, B12 and proteins [68,141]
Cortical brain atrophy [184,185]	Degenerative age related atrophy HIV encephalitis Hypoxic ischemic encephalopathy Malnutrition	Headache Tremors Loss of memory	-Treatment of offending cause -Mainly supportive care. -Nutritional supplements involving Vitamin B1, B12 and proteins [65]
Brain hemiatrophy [186]	Sturge Weber syndrome Dyke-Davidoff Mason's syndrome [37] Tuberous sclerosis [118] Stroke or ischemia [187]	Headache One side body weakness Convulsions	-Mainly supportive involving anticonvulsant drugs [188]

liver cirrhosis and diabetics.

Most studies addressing brain atrophy were done in developed countries where most advanced imaging tools and software are available.

Demographic features of brain atrophy are another dimension contributing to the dynamic nature of this condition. There is an obvious asymmetrical distribution of risk factors for brain atrophy according to population age profile. This together with the lack of advanced neuroimaging tools such as MRI in most health facilities may contribute to the scarcity of information about brain atrophy and other neurodegenerative changes in respective population, indicating that more studies on brain atrophy are needed.

In this review, most studies have shown that brain atrophy, leukoariosis and stroke are major triplets defining neurodegenerative conditions of the brain. Other conditions like micro bleeds and perivascular spaces (Virchow Robins spaces) are additional features that seldom occur.

Brain atrophy and stroke may occur among children in some conditions such asavitaminosis B1 and B12, protein-energy malnutrition, HIV encephalopathy, birth asphyxia, and sickle cell disease. Nevertheless, leokoariosis is very rare in children. Hypomyelination is more common due to genetic metabolism error such as Metachromatic leukodystrophy [198], Krabbe disease [199], Alexander disease [200] and adrenal leukodystrophy [201]. Even in demyelinative conditions like progressive multifocal leukoencephalopathy which happens in 1% of HIV patients, the condition is rare in children. Although studies suggests PML results from reactivation of the JC virus (John Cunningham virus) after immunodeficiency, the high multiplication rate of white matter in children from 2 to 10 years [50] needs to be investigated as a factors that may lower propensity for demyelination, a process which reduce brain volume by destruction of white matter [202].

When brain atrophy occurs in childhood, most clinicians tend to be attentive to investigate further, but when atrophy happens in the elderly it is frequently assumed to be part of the normal aging process. The biggest challenge is to differentiate the normal aging atrophy from the abnormal or pathological brain atrophy in the elderly population. A publication by Ferreira et al has addressed this challenge by differentiating visual qualitative assessment of Global Cortical Atrophy using scale from 0 to 3. It is suggested that at the reference age of 75 years; a GCA of 0 means the brain is normal. A GCA 1 (widened sulci) score represents mild atrophy, while a GCA 2 (volume loss gyri) score represents moderate atrophy at less than 75 years of age, while a GCA 3 (knife blade) score represents severe brain atrophy and is always abnormal irrespective of age [159]. In healthy children, brain atrophy is unprecedented due to an increase in white matter throughout the brain [203].

The type of brain atrophy is another important part of this review, as it has been shown that different etiological mechanisms of brain atrophy results in a certain patterns of brain volume loss. These patterns may help in singling out the most probable cause of brain damage. While some causes are reversible, some remains irreversible. Knowing the etiologies is a key element of brain atrophy management.

Most vitamins published in line with causes of brain atrophy such as Thiamine, Cobalamine and Folate are water soluble. Therefore, it is obvious that their serum levels fluctuate at different points in time. Low serum levels may not be exclusively considered as the cause of brain atrophy at that time. These ingredients need to be further quantitatively explored in order to establish their time-line for deficiency in human the body.

11. Conclusions and future prospects

From the extensive literature search that was completed, the following conclusions can be drawn. Brain atrophy is a neurodegenerative change of multi entity etiology commonly found with age advancement due to multi organ system involvement.

Brain atrophy, leukoariosis and stroke form the cardinal triplets of neurodegenerative changes. Leukoariosis happens rarely without atrophy and the likelihood of stroke occurrence is higher with the increase in volume of confluent white matter changes of leukoariosis.

Water soluble vitamin B1 and B12 cannot be directly pinpointed in causation of brain atrophy by virtual of their serum level instability but they should be integrated into managing brain atrophy reversibility.

Radiological quantification of brain volume by designed manual or automated techniques must always aim to reasonably achieve individualization of brain volume by considering a wide variation of cranial size based on among others gender and age variation. Brain atrophy is likely when an individual's brain volume shows significant deviation from one's own cranial volume.

Brain mapping and neurofeedback therapy have a promising future for integrating radiodiagnosis with interventions. It is time for

radiologists to extend their scope of knowledge beyond image interpretation as multidisciplinary clinical care is inevitable.

12. Recommendations

Early neonatal and infancy trans-cranial ultrasound examinations are suggested and should possibly be implemented in primary health care program in order to identify infants with possible intracranial anomalies and high intracranial pressure conditions such as hydrocephalus in order that such conditions can be managed in timely manner before brain atrophy develops.

Medical professionals such as radiologists, neurologists and neurosurgeons should be trained for various techniques of quantifying brain atrophy in order to establish tangible evidence of brain volume changes in the course of patients' management.

Multi sectoral and multidisciplinary interactions and planning system should be embraced in order to prevent and manage brain atrophy and other healthy conditions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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