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Pivotal Role of Aβ Amyloidosis in the Pathogenesis of Alzheimer's Disease, Cerebral Amyloid Angiopathy, and Lobar Haemorrhages: An Indication for Routine Plasma Aβ42/40 Ratio Screening in Trisomy 21

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Abstract

Aβ amyloidosis plays a pivotal role in the development of Alzheimer's disease, cerebral amyloid angiopathy, and lobar hemorrhages all of which have severe neurological consequences. Association between trisomy 21 and Aβ amyloidosis has been established posing patients with trisomy 21 risk of developing Alzheimer's disease, cerebral amyloid angiopathy, and lobar hemorrhages. Early detection of evidence Aβ amyloidosis in these patients will be very helpful in the management and overall outcome of such diseases. Research has shown the correlation between plasma or CSF Aβ42/40 ratio and Aβ amyloidosis, screening for plasma Aβ42/40 ratio in patients with trisomy 21 will aid in early detection of Aβ amyloidosis and secondary prevention of Alzheimer's disease, cerebral amyloid angiopathy and lobar hemorrhages in those patients.

Keywords: Aβ amyloidosis; Aβ42/40 ratio; Trisomy 21; Down syndrome; Alzheimer's disease; Cerebral amyloid angiopathy; Lobar hemorrhage

Introduction

Aβ amyloidosis is the accumulation of abnormally folded amyloid β protein which's a β2-macroglobulin in the tissue [1]. Abnormal amyloid β proteins commonly accumulate in the brain tissue forming an extracellular amyloid plaque [2]. These plaques usually arise from a precursor protein known as an Amyloid Precursor Protein (APP), which then is cleaved by enzymes beta-secretase and gamma-secretase to yield Aβ in a cholesterol dependent process and substrate presentation, and this played an important role in the pathogenesis of Alzheimer's disease [3]. Aβ molecules can aggregate to form flexible soluble oligomers which may exist in several forms. It is now believed that certain misfolded oligomers, these are often referred to as seeds, can induce other Aβ molecules to also take the misfolded oligomeric form, leading to a chain reaction similar to prion infection [4].

The physiological functions of APP remain not clearly defined, it's been found to play an essential role in brain development, memory, and synaptic plasticity [5,6]. Not only can it protect the neurons but also modulates intercellular interactions, regulation of neuronal growth, and synaptic plasticity [7]. Mutations in the *APP* gene have been shown to increase the synthesis of Aβ amyloid protein, which forms senile plaques and causes degenerative changes in peripheral neurons [8]. These mutations in the transmembrane region of the amyloid precursor protein have been reported to alter the ratio of residue 42 of Aβ protein (Aβ42) and residue of 40 Aβ proteins (Aβ40) [9]. This alteration in the ratio of Aβ40 and Aβ42 could be assayed in the plasma, which can be helpful in the noninvasive diagnosis of Aβ amyloidosis and also in a screening of people with a high risk of Aβ amyloidosis such as people with trisomy 21 (Down's syndrome). This will be preferable in the screening of Aβ amyloidosis in these people to invasive options available such as biopsy.

People with trisomy 21 (Down's syndrome) have been reported to have a higher risk of developing Aβ amyloidosis, but the mechanism for this has not been fully understood [10]. However, a report was made on the triplication of the *APP* gene on the extra copy of chromosome 21 to play an important role in the pathogenesis the amyloidosis in them [11]. The effect of trisomy 21 on Aβ amyloidosis was also found to correlate with a shift in Aβ40/42 ratio.

Literature Review

Aβ amyloidosis in the pathogenesis of Alzheimer's disease, cerebral amyloid angiopathy, and lobar haemorrhages

It has been found that nerve cells produce more Aβ than other cell types in the human body, which play important roles in normal physiological activities of the central nervous system, such as intercellular signaling [12]. So, Aβ amyloidosis which was established earlier to be common among people with trisomy 21; affects the brain predominantly, and can manifest as either alzheimer's disease, cerebral amyloid angiopathy, lobar hemorrhages, or a combination of any. The role of Aβ amyloidosis in the pathogenesis of these diseases includes.

Alzheimer's disease: Alzheimer's disease is a neurodegenerative disorder characterized by progressive dementia and insidious impairment of higher cognitive functions [13]. Amyloid plaques formed by extracellular accumulation of Aβ amyloid linked to a mutation in the amyloid precursor protein *APP* gene has noted in the pathogenesis of Alzheimer's disease [14]. In the brains of patients with Alzheimer's disease, it's been found that β-amyloid proteins penetrate the cell membrane, triggering a series of pathological events and ultimately leading to cellular dysfunction and death [15,16]. Generation of reactive oxygen species leading to oxidative is one of

the mechanisms by which Aβ amyloidosis is neurotoxic, the amyloid plaque consists of Aβ aggregate and metallic ions e.g. copper and iron which generate the reactive oxygen species [17].

Aβ amyloidosis has been found to cause aberrant phosphorylation of tau protein which is microtubules associated protein found in the brain through Aβ-induced activation of p38 MAPK activity which accelerates the spatiotemporal progression of tau pathology leading to the formation of neurofibrillary tangles, and increases the formation of amyloid plaques; these are essential hallmarks of Alzheimer's disease [18].

Cerebral amyloid angiopathy and lobar haemorrhages

Cerebral amyloid angiopathy is one of the important cerebral small vascular diseases and also a common risk factor associated with lobar hemorrhages in elderly people and age related cognitive decline, it's an amyloidogenic peptide mostly the same as those found in Alzheimer's disease, especially Aβ40 [19]. The pathogenesis of CAA is unknown to a large extent, however, it is known that in most cases the disease is due to an abnormal production or impaired clearance of the Amyloid Beta protein (Aβ), a cleavage product of the Amyloid Precursor Protein (APP) leading to deposition and accumulation in the walls of the small and medium-caliber leptomeningeal and cortical arteries [20]. Resulting from abnormal production together with failure in clearance, the accumulation of Aβ is firmly involved in damage to the blood-brain barrier and small cerebral vessels.

Aβ accumulation has been found to induce the production of Reactive Oxygen Species (ROS) through the NADPH oxidase pathway, leading to altered tight junction expression and localization. It was demonstrated by Carrano, et al., that Aβ42 induces toxicity through Receptor Advance Glycation End products (RAGE) mediated ROS production and downregulation of tight junction proteins such as occludin, claudin-5, and zona occluden-1. In addition, the effects of Aβ amyloidosis on different brain capillary endothelial cells from different sources such as rats, bovine, and mice when use in development not a blood-brain barrier *in vitro* studies have been shown to cause increased permeability. All these effects of Aβ amyloidosis on cerebral vessels and the blood-brain barrier leading to lobar hemorrhages. Patients with CAA could present with hemorrhagic stroke, ischemic stroke, cognitive impairment, and transient neurological symptoms. CAA associated intracerebral hemorrhage can present as lobar macro hemorrhages, cortical micro hemorrhages, or subarachnoid hemorrhage with the lobar hemorrhage involving mainly the cortical and subcortical areas and has a predilection for occipital and temporal lobe but can affect any part of the brain. CAA was included in the SMASH-U criteria (structural lesions, medication, amyloid angiopathy, systemic diseases, hypertension, undetermined) for etiological classification of intracerebral hemorrhage; showing the importance of CAA in the development of lobar hemorrhage. Cerebral amyloid angiopathy-related lobar hemorrhage was found to have a predilection for the frontal and parietal lobes of the cerebral hemisphere, affecting the cognitive functions of the patient.

Two types of cerebral amyloid angiopathy have been reported, CAA-type 1 involves Aβ amyloid deposition of the leptomeningeal and cortical arteries, cortical capillaries, arterioles, veins, and venules while CAA type 2 Aβ amyloid deposition in each of the above structures except for cortical capillaries; amyloid deposits are detected through immunohistochemistry. No significant differences in severity, age at presentation, and area of infarction were reported between the two types, just that type 2 was relatively common.

Aβ42/40 in Aβ amyloidosis

Enzymatic cleavage of β-Amyloid Precursor Protein (APP) results in the formation of A peptides, which constitute the primary component of senile plaques. The sequential processing of APP by β-site Amyloid precursor protein Cleaving Enzyme 1 (BACE1) and β-secretase results in the formation of Aβ amyloid. There are several Aβ peptide isoforms released. About 5%–10% of all Aβ isoforms in the CSF are the Aβ42 isoform, which ends at position 42 on the amino acid chain.

Studies have shown that the level of CSF Aβ42 amyloid protein correlates inversely with amyloid plaque load as found in autopsies or with Positron Emission Tomography (PET). Indeed, Aβ42 is a major component of the plaques in the brains of Alzheimer's disease patients. However, other diseases without plaques, such as bacterial meningitis, also have lower CSF Aβ42 concentrations. As a result, the theory presented does not fully explain the selective decrease in CSF Aβ42 concentration. Reduced Aβ42 generation, increased Aβ42 degeneration, or oligomerization of monomers are three possible hypotheses supporting the role of a decrease in Aβ42 concentration in the pathogenesis of Aβ amyloidosis.

Aβ40 being the most abundant isomer of Aβ amyloid protein was found to useful when its level is compared to Aβ42 (Aβ42/40 ratio) in diagnosing Alzheimer's disease than Aβ42 level is used alone. As a result, several medical facilities around the world began routinely employing Aβ42/40 as a diagnostic tool around the year 2015. Since then, dozens of studies, as recently reviewed in, have confirmed that the Aβ42/40 ratio performs better as a diagnostic and prognostic biomarker for Alzheimer's Disease (AD) than the Aβ1-42 ratio. Three broad categories can be applied to all of these reports.

- AD diagnostic studies, including those that use the clinical diagnosis as a reference (case-control design), as well as those that compare AD pathology to other modalities like amyloid PET.
- Research on the differential diagnosis of AD in comparison to other neurodegenerative disorders.
- Prognostic studies, in which the ability of the Aβ-42/40 ratio to predict the progression of the disorder from the pre-clinical to the dementia stage was examined.

For instance, various Aβ-PET tracers showed consistency in the concentration of CSF biomarkers and Aβ-PET traces. In studies of AD patients and cognitively normal people, an inverse, non-linear association was found between Aβ42 and amyloid PET using the Pittsburgh compound B (PiB), but not between Aβ40 and amyloid PET. The discordance between CSF Aβ42 levels and PET imaging-positive results is also known, despite the well-established high concordance between CSF Aβ42 levels and amyloid-PET imaging. As discordant results are more common in cognitively normal people the two modalities may provide information that is partially independent of one another. When Aβ42/40 ratio replaces Aβ42 as a reference, the concordance of the CSF results with PET imaging significantly improves (from approximately 75% to approximately 90%). In addition, evidence indicating that CSF Aβ42 is a more sensitive marker of Alzheimer's disease at very early stages than amyloid-β is detectable with PET imaging suggests that A PET may be used for better grading of early Alzheimer's disease.

Aβ40 level was found to be reduced in Cerebral Amyloid Angiopathy (CAA), the Aβ42/40 ratio can also be used to differentiate Alzheimer's disease from cerebral amyloid angiopathy. Based on the presence of auto-antibodies against Aβ40 and Aβ42 and the most common clinical improvement observed in response to immunosuppressive treatment, it has been hypothesized that CAA is triggered by vascular Aβ amyloid deposition followed by an Aβ-directed (auto)immune response. CAA has been associated with elevated total and phosphorylated tau (t-tau and p-tau) concentrations in the Cerebrospinal Fluid (CSF). Aβ40 levels, in particular, appeared to be of clinical interest in distinguishing CAA from AD. CSF concentrations of these biomarkers have, to our knowledge, only been examined once in a series of CAA patients.

When compared to the other disorders, Aβ42 appeared to be the most specific CAA associated inflammation (CAA-I) biomarker. A study found that Aβ42 levels in CAA associated inflammation were significantly lower than those in CAA, and control subjects, but not AD. However, there was significant overlap in the levels of Aβ42 and Aβ40 between the various amyloid related conditions, making individual patient interpretation challenging, and age may alter CSF biomarkers, particularly Aβ42. Researchers and clinicians should keep in mind that amyloid may also play a role in other inflammatory and infectious CNS disorders (such as multiple sclerosis and the human immunodeficiency virus) that are typically unrelated to primary amyloid related pathophysiological processes. The brain's dynamic equilibrium of Aβ production, clearance, and accumulation results in A concentrations in the CSF. While predominant deposition of Aβ42 in diffuse senile plaques in AD likely results in selective reduction of CSF Aβ42 levels, both Aβ40 and Aβ42 are probably trapped in the cerebral vasculature in CAA. In Alzheimer's disease, brain retention of amyloid tracers like PiB is higher, but CSF levels of amyloid-β42 are lower. This is thought to be because brain soluble amyloid-β42 is sequestered into insoluble plaques, making less amyloid-β42 available for clearance into the CSF. Although this inverse relationship has generally been observed between both measures, a subset of cases show discordant results, with either abnormal CSF amyloid-β42 but normal amyloid PET, or normal CSF amyloid-β42 but abnormal amyloid PET. This inverse relationship has been confirmed by many groups across subjects with cognitively normal, Mild Cognitive Impairment (MCI), and Alzheimer's disease. Isolated PET positivity has been reported in both MCI and Alzheimer's disease, although discordance in subjects with normal amyloid PET is typically caused by abnormal CSF amyloid-β42. A decreased CSF Aβ42, a 42-amino acid long protein, has been consistently found in the CSF of AD patients, allowing for discrimination from healthy older controls with a specificity and sensitivity of between 80% and 90%.

Discussion

Plasma Aβ42/40 ratio as a screening investigation in Aβ amyloidosis

Assaying the plasma level of the Aβ42/40 ratio will be a convenient way of screening for Aβ amyloidosis, studies have shown that its value correlates with that of CSF and neuroimaging in Alzheimer's disease. A study used validated Enzyme Linked Immunosorbent Assays (ELISAs) to evaluate the Aβ42/40 plasma ratio, separating the peptide fractions that are free in plasma (FP42/40) from the total Aβ peptides in plasma (TP42/40) and the amount of Aβ that is bound to other plasma components (BP42/40). The study evaluated the potential of plasma Aβ ratios as enrichment tools for secondary prevention clinical trials by examining the cross-sectional and longitudinal association of these plasma markers with brain Aβ-PET results, as well as their diagnostic performance and capacity to predict brain Aβ deposition trajectories. Researchers found an association between low plasma Aβ42/40 ratio with cognitive decline in the elderly without dementia and an increased risk of developing Alzheimer's disease. Inconsistencies in sample handling may lessen the likelihood of bias in single Aβ peptide levels when Aβ42/40 ratios are used in place of single Aβ peptide measurements. In line with this, recent CSF studies have shown that the Aβ42/40 ratio performs better diagnostically than Aβ42 alone. Also, plasma Aβ42/40 ratio alone or when combined with FDG-PET can accurately predict amyloid-PET positivity. This shows how effective the plasma Aβ42/40 ratios are in screening for Aβ amyloidosis in people with risk while other investigations such as CSF Aβ42/40 ratio and neuroimaging can be used in confirming the diagnosis.

Benefit of screening for Aβ amyloidosis in trisomy 21

Amyloid-β starts to build up in the brains of some people with Down syndrome as early as childhood, and by the middle of their 20's, most of them will have accumulated a lot of it. By the time they are 40, people with Down syndrome will also all have neurofibrillary tangles that have developed in a pattern that is roughly comparable to that of Alzheimer's disease in the general population.

Screening for Aβ amyloidosis serves as means of secondary prevention of Alzheimer's disease, cerebral amyloid angiopathy, and lobar hemorrhages among patients with trisomy 21 which is at risk.

Screening for Aβ amyloidosis can also be used to monitor the progress of the disease and also to prevent other comorbidities, this can also aid in making a therapeutic decision. Overall, screening for Aβ amyloidosis will improve the quality of life of people with trisomy 21.

Conclusion

The number of people living with trisomy 21 is increasing, and research that looks into improving the quality of life of these people should be encouraged. With the association between trisomy 21 and Aβ amyloidosis being fully established, the therapeutic targets should be towards reducing the complications that may result from this association.

Early detection of Aβ amyloidosis will help in the prevention of some conditions such as Alzheimer's disease, cerebral amyloid angiopathy, and lobar hemorrhages in people with trisomy 21. Screening through plasma Aβ42/40 ratio will aid early detection of Aβ amyloidosis which can be confirmed through CSF Aβ42/40 ratio, neuroimaging, or biopsy. With plasma Aβ42/40 ratio easier to assay, this research suggests that every patient with trisomy 21 should be regularly screened and prompt therapeutic decisions should be made upon detection of any deviation from the normal assay.

Conflict of Interest

The authors declared no conflicts of interest.

Ethics Approval

Not applicable.

Consent to Participate

Not applicable.

Consent for Publication

The authors gave their consent to publish the article.

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Authors' Contributions

- **Kehinde Alare:** Conceptulization, project administration, writing-review and designing.
- **Kehinde Alare:** Collection and assembly of data.
- **Kehinde Alare:** Reviewed and edited the final draft
- **Manuscript writing:** All authors.
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