Scientia Psychiatrica
Journal Homepage: www.scientiapsychiatrica.com
eISSN (Online): 2715-9736

Alzheimer's Disease in Individuals with Down Syndrome

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ARTICLE INFO

Keywords:
Alzheimer's disease
Down syndrome
Trisomy 21

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The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/scipsy.v4i2.117

A B S T R A C T

Down syndrome (DS) is a genetic disorder that occurs due to trisomy on chromosome 21. It is known to relate to the amyloid-beta (A4) precursor protein (APP) gene and amyloid plaques, affecting developmental processes and resulting in early dementia, signifying a relation to Alzheimer's disease (AD). AD in individuals with DS affects many aspects include memory function, social and cognitive behavior. There is also a high likelihood for individuals with DS to have an AD at an early age, adding more challenges to the patients and the caregivers. Triplication of the gene in DS and an extra copy of APP in familial AD patients are responsible for the genetic link between these two diseases.

1. Introduction

Trisomy 21 serves as a model to understand the result of supernumerary copies in the human genome.[1,2] One of the Challenges for DS individuals who survive to old age is a high risk for a developing onset of Alzheimer's disease (AD) at an early age.[2] It is thought the APP gene, amyloid precursor protein, is present on chromosome 21, and trisomy of the chromosome leads to overexpression of the APP gene and increases the development of amyloid plaques.[3] Other than memory, language, executive function, and motor coordination problems, cognitive impairment can also develop in people with DS. The presentation may vary significantly due to advanced age or other risk factors that lead to increased development of dementia.[4] Brain damage by certain diseases can cause dementia, one of which can be caused by Alzheimer's disease. Some early behavioral changes and cognition-related symptoms in individuals with DS and AD include sadness, anxiety, low enthusiasm, aggressiveness, irritability, uncooperativeness, and inattentiveness.[3] Due to the dramatic increase of life expectancy in the DS population, from 12 years in 1942 to 60 years in 2003, revealing early-onset dementia proved necessary to prevent cognitive deterioration.[5] This is supported later by the finding that dementia is more likely to be found in DS individuals more than 50 years old compared to the general population of the same age.[2] This literature review intends to discuss the genetic relationship between these two conditions.

Down syndrome (DS is a genetic disorder and one of the most common causes of intellectual incapacity, affecting 1 of every 650 to 1000 live births. Due to

advancements in medicine, DS individuals increasingly survive old age. However, by increasing age, there are also parallel increase risk of developing early Alzheimer's disease (AD), possibly because trisomy 21 leads to overexpression of the APP gene and increases the development of amyloid plaques.[1,2] It's Almost 100% of all individuals with down syndrome who survive to 60 years old show neuropathological changes consistent with AD. The Prevalence on ages 35-49 years old is 9-23%, 50-59 years old is 55% and above 60 years old is 75%-100%. The Prevalence of AD in DS adults may be affected by gender, although the result has been inconsistent and still needs to be studied further. In Mhatre, PG et al. found that men with DS had a greater risk 6 times of developing AD compared to women with DS (Hazard ratio=6,32), but the difference in risk is only seen at the age of over 60 years. There were two other studies that showed a different result. They found that women have a greater risk of developing AD than men.[23,24] However, the result hasn't been replicated by other studies, which have found no difference. Our literature review intends to examine down syndrome and Alzheimer's disease development.[25,26]

Alzheimer's disease in individuals with down syndrome

Down syndrome is a genetic disorder with the presence of an extra (third) chromosome 21. Down syndrome is associated with various structural and functional abnormalities making people with DS highly susceptible to having another disorder/disease by aging, such as AD.[17] Individuals with DS seem to be at a significant likelihood of having AD at such an early age.[18] The characteristic of sporadic dementia around 60 years old of which Alzheimer's disease related to down syndrome can be found in 5-60 years old patients whereas 40-80% down syndrome population.[18] there were so many neuropathological studies that nearly proved off all Down Syndrome patients older than 35 years old developing into AD neuropathology.

Neuropathology Alzheimer's Disease identified with age is a cerebrum picture in patients with Down condition children upon entering the world for the most part ordinary, however, improvement after birth dials back. Until this point in time, our insight into the mind anomalies seen in Down condition is put together straightforwardly with respect to post-mortem examinations. Posthumous imaging of the cerebrums of individuals with Down disorder has created various neuropathological discoveries, the most outstanding of which are cerebrum weight reduction, front facing and fleeting flap hypoplasia, decay. cortical support, cerebral ventriculomegaly, cerebellum, and cerebellar hypoplasia, particularly in the physical space of the center projection. Interestingly, subcortical districts, like the lenticular cores and the back parietal and occipital cortical dim matter, have genuinely normal cerebrum volumes.[2]

At the point when a positron discharge tomography was performed to decide a huge expansion in amyloid, there were indications of a psychological decrease in patients with Down condition. The entorhinal cortex, which then, at that point spreads to the hippocampus and remembers neocortical destinations for the further developed period of the infection, turns into the underlying objective for obsessive results in patients with Down disorder. This pathology tops in adolescence (around 8 years old) yet increments measurably somewhere in the range of 35 and 45 years old and is related to NFT. The obsessive contrasts between Alzheimer's patients with Down's condition were all the more early plaques and tangles in the hippocampus contrasted with patients with beginning phase Alzheimer's and late-beginning Alzheimer's in non-Down disorder patients.[2]

When we are talking about symptoms of AD in DS, especially including the neuropathology theme, so there is a lot of manifestation which take a part in the develepment of disease. At birth, generally brain morphology in people with DS is normal, but postnatal development is experienced. Several neuropathological findings have been found in postmortem DS people, among which the most noticeable are hypoplastic

frontal and temporal lobe gross brain weight loss, cortical gyrus, cerebral ventriculomegaly, cerebellar atrophy, and cerebellar hypoplasia, especially in the middle lobe. There is a drastic reduction in hippocampal volume, while the amygdala does not decrease in volume beyond the size of the overall brain volume. Regardless of the amnesia experienced, DS patients who died over the age of 40 years, they performed a postmortem examination and showed that there was an accumulation of deposits of protein Aβ in senile extracellular plaques (SPs) and perivasular amyloid (amyloid angiopathy).[2]

The initial pathology that occurs in DS begins in childhood (8 years), namely the accumulation of Aβ in the entorhinal cortex which then spreads to the hippocampus then at a more advanced stage can spread to the neocortex. This pathology progresses rapidly between the ages of 35 and 45 years and becomes associated with NFT. In AD-DS patients there is an increase in the rate of glucose metabolism that occurs in the temporal cortex on functional brain examination. This suggests that a 15% increase in compensatory response may occur in the temporal lobe with age. At the age of about 45 years, the prevalence of dementia increases by 75%. Memory loss in AD-DS patients is a common symptom that most often occurs. According to the study, the comparison between behavioral and emotional changes performed on AD and non-AD DS patients showed that psychotic behavior in AD-DS was too severe. They have very few hallucinations and delusions. Symptoms that are more prominent are physical movements, the behavior they show is maladaptive such as restlessness, sleep disturbances, and cannot be cooperative when spoken to. This cognitive impairment results in impaired skills in daily activities, namely in taking care of oneself such as eating and bathing. Misrecognition or impaired social communication is an early symptom of frontal lobe dysfunction in DS patients with AD. Several studies have shown that seizures are the most common symptom found in DS with AD in people over 60 years of age. Other symptoms include personality changes, focal neurological signs, apathy and loss of the ability to speak.[2]

Dyspraxia which is a symptom of a deficit in which the reduced capacity to use the leg properly for ambulation does not interfere with sensory or motor disturbances. Dyspraxia is a common symptom that is often experienced at first in DS-AD patients. The mechanisms between dyspraxia and dementia symptoms over time are interrelated. Symptoms of epilepsy in DS-AD patients also increased by 46% with age. The onset of seizures is experienced by about 40% of patients before the age of 1 year, and the other 40% begins at the age of 30 years and over.[2]

Manifestations of seizures at a young age are more common in DS. Where the type of seizure that often occurs is tonic-clonic seizures with myoclonus. While at an older age the types of seizures that often appear are simple or complex partial seizures. In DS, myoclonic epilepsy can occur in the slow system, namely when waking up is characterized by myoclonic jerks, generalized tonic-clonic seizures, and disturbances in EEG waves. According to the study, these all related to chromosome 21.[2] Decreased progressive cognitive and motor function of the brain in DS patients is associated with the occurrence of epilepsy experienced by the patient. Some conclusions conclude that the daily changes experienced by DS patients will cause activity, and symptoms such as dementia, withdrawal from social interactions, unstable emotions, and apathy are symptoms to watch out for from these neurological disorders.[2] The amyloid cascade hypothesis was a profound explanation for understanding such risk. On the other hand, the influencing of additional genetic and environmental variables will take part in the onset and progression on those.[20]

According to the amyloid cascade theory, AD with early-onset is related to the presenilin genes and amyloid precursor protein (APP).[18] Triplication of the amyloid-beta (A4) precursor protein (APP) gene in Down syndrome people, as well as an extra copy of APP in familial AD patients, appear to be responsible for the genetic link between these two diseases.[19] This results in overproduction of APP intermediate product,

amyloid β (Aβ), leading to increased accumulation in the brain.[3] This overproduction also accelerates downstream neurodegeneration, disturbs synapses signal, causes nerve cell death, tissue damage, and brain mass reduction at the end.[20,21] Furthermore, studies show that these processes are only found in full trisomy 21 conditions, so that partial trisomy 21 and APP disomic condition will not show APP overexpression in AD pathogenesis.[22]

Cerebral atrophy is a general feature of Down's and Alzheimer's patients. In pathological findings, there are also Aβ deposits in extracellular senile plaques and intraneuronal neurofibrillary tangles. Most people with Down syndrome will experience the manifestation of Alzheimer's disease at the age range of 50-60 years.[21] when we are talking about variables on both in the general population and in Down Syndrome patients so that it could be related to the degree of Ab pathology, like apolipoprotein E (ApoE) genetic status.[22]

Genetics (heredity) plays an important role in increasing the risk factors for Alzheimer's dementia, where two types of genes play a role in developing Alzheimer's. Genes are risk genes, and determinant genes are two different types. A risk gene that increases the likelihood of disease progression but does not guarantee disease occurrence is apolipoprotein E 4. While the determinant genes directly cause Alzheimer's dementia to consist of proteins, presenilin-2 (PSEN-2) and presenilin-1 (PSEN-1), and lastly, amyloid precursor protein (APP).[31,32] Alzheimer's disease caused by all three determinants is called autosomal dominant Alzheimer's disease (ADAD). Alzheimer's dementia is characterized by progressive atrophy and gliosis of the temporal lobes and hippocampus, another associated Cortex, and the primary motor and sensory cortex.[31] Alzheimer's dementia has histopathological characteristics, namely the discovery of extracellular eosinophilic deposits of amyloid consisting of Aβ peptide (APP clearance product) called amyloid plaques and intraneuronal aggregates of protein-associated microtubules (neurofibrillary tangles).[32]

Polymorphisms, PSEN-1, PSEN-2, and APP, are mostly associated with cause to early-stage onset Alzheimer's disease. Periodically, variant four, the apolipoprotein E, is strongly associated with a doubled risk of late-stage onset AD.[34] Mutations in the following genes cause rapid onset autosomal dominant Alzheimer's dementia, namely APP gene on 21 chrome, the presenilin-1 gene on 14 chromosomes, and the PSEN-2 on chromosome 1. These three genes lead to overproduction of the 42 amino acid peptide form over the 40 amino acid form. This results in neuronal death, loss of synapses, and formation of NFTs and SPs. The apolipoprotein E 4 genotype without polymorphisms in other genes was associated with late-onset Alzheimer's dementia.[35]

The gene placed on chromosome 21 is amyloid precursor protein which is differential splicing results in four kinds of the APP. The beta/A4 protein, a major constituent of senile plaque, is a 42-amino acid peptide cleaved from the amyloid precursor protein. In DS (trisomy 21), three templates were found of protein gene, and in disorder with an amyloid precursor protein gene at codon 717. This pathway of pathological results in more deposition of the beta/A4 protein. How the process that occurs in the amyloid precursor protein in its role as the main cause of Alzheimer's disease is still unknown.[27] A study demonstrated the potential function of the E4 gene in the course of Alzheimer's disease. Individuals with single-gene transcription are three times more likely than individuals without the E4 gene, and individuals with two copies of the E4 gene are eight times happens than those without the gene. Diagnostic testing of this kind of gene is not probable because the gene can be found in other individuals, although, in all people, dementia and is not necessarily seen.[27]

Amyloids are peptide as well as protein aggregates which develop when normal soluble proteins misfold, causing them to adhere together owing to its chemical characteristics but also build within organs and extracellular compartments. Fibrous formations created by amyloids as well as plaques which are extremely insoluble and resistant to degradation, and

they have a role in a variety of illnesses including AD, spongiform encephalopathies, type II diabetes and Down syndrome (DS). The plaques of amyloid linked to Alzheimer's disease are made up of peptides generated from the incorrect amyloid precursor protein (APP) processing, which is a protein known to normally sits near nerve cells. Beta amyloids seem to be toxic peptide fragments. The plaques of amyloid form in tissue of brain, destroying neuronal connections and disrupting synapses signaling, resulting to tissue loss, nerve cell death, also decrease in brain mass in Alzheimer's disease. The immune system and inflammatory responses are triggered by smaller clumps of beta-amyloid rather than the plaques themselves.[21] Amyloid beta (Aβ) seems to be one of byproduct of the APP proteolysis pathways, in which APP is cleaved by gamma-secretase and beta-secretase1. The Aβ42 version is especially susceptible to aggregation, forming beta sheets which are accountable causing plaques of amyloid. As complement to the fibrillar form, there may be oligomer forms of Aβ42 that could be much more damaging to neurons.[20]

People with DS are more likely than the general population to acquire Alzheimer's disease (AD) due to overexpression of the amyloid precursor protein gene on chromosome 21, which causes an early start as well as fast buildup of amyloid protein (Aβ) with time. 3 Since this buildup of the plaques of amyloid in the brain has been the major pathogenic feature of the illness, the precise connection involving tau neurofibrillary tangles and plaques, cognitive symptoms, and neurodegeneration is yet unknown.[22] Several people having Down Syndrome begin to collect Aβ in their brain throughout infancy and adolescence, and the majority of them will have formed significant quantities of scattered Aβ plaques by the age of 20. Aβ plaques and tau neurofibrillary tangles can have accumulated over time, and by the age of 40, each person with Down Syndrome will already have reached levels adequate for a pathological diagnosis of Alzheimer's disease.[22]

The increased synthesis of amyloid beta (Aβ) protein, which leads to amyloid deposition in the brain, has been linked primarily to the overexpression and triplication of the genes responsible for amyloid precursor protein, which is found on chromosome 21.[4] Aβ is derived from amyloid precursor protein, that is often triplicated in DS. Beta and gamma secretases is sequentially cleaves the amyloid precursor protein (which coded for by Presenilin 1 PSEN1 and Presenilin 2 PSEN2 genes) in the amyloidogenic pathway to release Aβ, that creates aggregates and toxic conformations, resulting in characteristic clinical symptoms of AD. APP overexpression is considered the primary mechanism which causes deposition of Aβ in DS.[22]

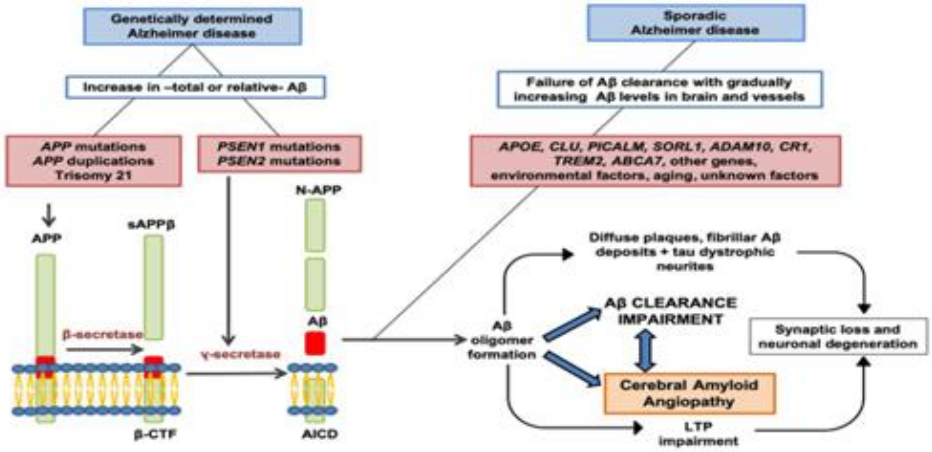

Figure 1. The balance of APP clearance and processing in a model of AD pathogenesis [22]

Aβ deposition in the brain is one of the implications of the pathogenesis of Alzheimer's disease. Accumulation of Aβ (especially Aβ42 peptide) in the brain is the initiation of neuronal dysfunction, neurodegeneration, and dementia.[28,29,30] Mutations in the APP genes on C21, PS1 on chromosome 14, and PS2 on chromosome 1 lead to early-onset familial Alzheimer's disease that results in overproduction and increased aggregation of Aβ. Beta-Amyloid is a physiological product of APP normal and is a soluble compartment of plasma and cerebrospinal fluid.[29] In the formation of Aβ, APP is broken down by three enzymes, namely -, -, and -secretase. The cleavage of APP by -secretase and then by -secretase produces Aβ while it is broken down by -secretase will produce nontoxic peptides.[28,33]

Multiple mutations in APP lead to increased Aβ due to the cleavage of APP by increased -secretase. Beta-Amyloid peptide is the most affect protein component in a plaque of neuritic that are apparently of Alzheimer's disease.[28] Beta-Amyloid sometimes initiates toxic action before fibril formation. Elevated levels of soluble A rather than plaque Aβ are associated with cognitive dysfunction in Alzheimer's disease. The presence of cognitive impairment in individuals with Alzheimer's is strongly associated with loss of synapses across cortical brain regions.[30,36] Self-aggregation of Aβ to low-n soluble oligomers is a major cause of synapse toxicity in Alzheimer's disease. Both carboxyl-terminal variants of Aβ, namely Aβ40, are the main secretory species of cultured cells and are present in the cerebrospinal fluid. At the same time, Aβ42 is the first part of a component of amyloid deposited in the brain in Alzheimer's disease. Increased Aβ42 more often aggregates and forms fibrils. The neurotoxicity produced by Aβ aggregation results in several mechanisms, such as accumulation of free radicals, dysregulation of calcium homeostasis, inflammatory response, and activation of several signaling paths.[35]

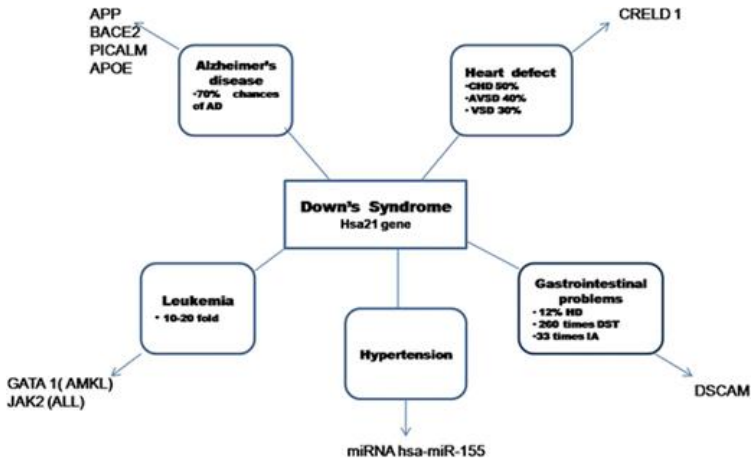

Figure 2. Various conditions downs' syndrome with its causative genom.[37]

Various mutations have been reported causing Alzheimer's in early type-onset. Some of the causative Genom explained in the current textbook are beta-secretase 2, Apolipoprotein E, APP, and Phosphatidylinositol binding clathrin assembly protein. APP is an integral protein barrier concentrated in the gaps of neurons, and trisomy of this protein takes a big part of the increasing sequence of dementia in Down syndrome patients. Three times multiplication of Hsa 21 along with APP in people without DS also been shown to be associated with early-onset AD.[38]

Individuals with down syndrome (DS) are at high risk of developing Alzheimer's disease (AD). Early

detection of dementia-related DS is needed for early intervention and management, but AD-DS diagnosis is still challenging related to the absence of validated and standardised diagnostic instruments.[39,42] Screening of dementia-related cognitive changes in Down's is a main difficulty because of their underlying deterioration cognitive function.[39] Current instruments which are used on dementia-DS screening should have abilities to determine cognitive and age-related changes, such as Dementia Questionnaire for Learning Difficulties (DLD). DLD is a frequently used informant-based screening instrument in clinical practice to measure dementia (cognitive and social deterioration) in DS population. Another instrument that can be used in dementia-DS screening is CAMCOG-DS (Cambridge Cognition Examination for Down Syndrome). CAMCOG-CG is an instrument that can differentiate cognitive performance between younger and older people with possible dementia, but this tool is recommended use together with other assessment to increase its reliability.[40]

Based on International Classification of Diseases, 10th Revision (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), dementia-DS diagnosis need several assessments in addition to cognitive evaluation. Behaviour changes as one of common signs that present earlier in AD-DS need to be assessed as part of screening aspect.[40]

Nowadays, blood-based biomarkers become one of choices on diagnosis approach including in diagnosis AD-DS. Detecting specific biomarkers of Alzheimer's, such as Aβ levels, can help on early diagnosis and be used as prediction/monitoring factor on disease course. Studies show that plasma Aβ1 (40 and 42) levels were found in higher concentration in DS individuals and also dementia-DS individuals. High level of Aβ40 and Aβ42, low Aβ42/Aβ40 can be used as dementia-DS biomarkers.[39,41,42] Plasma total tau (t-tau) and neurofilament light protein (NfL) concentrations is also found on higher level in DS. On Cerebrospinal fluid (CSF), low Aβ level, high tau level (t-tau and p-tau), and high level NfL are considered as Alzheimer's biomarker. Therefore, NfL detection, both in CSF or plasma, have diagnostic value as Alzheimer's biomarker.[43] In addition, apolipoprotein (APOE) genotype examination, including APOE E4 allele, also has a significant role on AD-DS screening. APOE E4 allele is one of marker on earlier AD onset and higher progression rate so that early APOE detection can be a good utility for early diagnosis and treatment.[40]

Management of individuals with Down syndrome related to Alzheimer's disease is a holistic therapy that involves a multidisciplinary and multi-institutional approach from various professional fields including specialist doctors for monitoring therapy, psychologists for cognitive assessments, special nurses, psychiatrists and other professionals such as occupational therapists or speech and language therapists.[44,45] The goals of this therapeutic management are to prevent and treat cognitive impairment, reduce intellectual disability and help patients carry out daily activities.[45] Treatment can be given pharmacologically as well as non-pharmacologically.[45] Most of pharmacological therapy is supportive therapy in adult patients, because basically the use of these drugs has no significant evidence of decreased cognitive function but reduced early symptoms and increased quality of life expectancy.[46] The treatment approach is based largely on the "cholinergic hypothesis" and the use of anticholinesterase inhibitors including donepenzil, galantamine, rivastigmine, and memantine have been used to treat Down syndrome-associated dementia.[46] The selective acetylcholinesterase inhibitors include galatamine and donepenzil, non-competitive NMDA antagonists is memantine, which belongs to the class of dual inhibitors between butyrylcholinesterase and AChE is rivastigmine.[47]

Table 1. Antidementia drugs and their profile.[47]

Medication	Chemical class	Action	Type of inhibiton	Route of administration	Frequency administration	Given with food	Dosage per day (mg)	Indication
Donepezil	Piperidine	AChE inhibitor	Rapidly reversible	Oral tablets	Once a day	No	5-10	Mild-moderate AD
Rivastigmine	Carbamate	Dual inhibitor BchE, AChE	Pseudoreversible	Oral capsules, oral solution and patches	Twice a day	Yes	6-12	Mild-moderate AD
Galantamine	Phenanthrene alkaloid	AChE inhibitor	Repidly reversible	Oral tablets	Twice a day	Yes	16-24	Mild-moderately severe AD
Memantine	Glutaminergic modulator	NMDA antagonist	N/A	Oral tablets and oral solution	Twice a day	No	10-20	Moderately Severe – severe AD

In the treatment of antidementia drugs, doctors and other medical teams who treat patients must be aware of the increase in the adverse effects of drugs. It has been reported that donepezil has an increased frequency of serious side effects, including a decrease in heart rate that in people with down syndrome becomes significant with pre-existing weak heart conditions, depression, gastric ulcer with bleeding and spasms.[4] In elderly patients, to reduce the side effects of these drugs, one of them is by starting low-dose therapy and increasing the dose slowly and gradually.[47]

Table 2. Conditions in which antidementia therapy must be aware of side effects. [47]

Drug	Condition
Donepezil	Chronic obstructive pulmonary disease (COPD), supraventricular heart rhythm disorders, past history of peptic ulcer, asthma, liver disfunction, and sick sinus syndrome.
rivastigmine	Impaired liver function, impaired kidney function, supraventricular heart rhythm disorders, asthma, gatric ulcers and chronic obstructive pulmonary disease (COPD).
galantamine	blocked urinary tract, supraventricular heart rhythm disorders, asthma, lung disease (COPD), impaired liver function and history of peptic ulcer.
memantine	impaired renal function, impaired cardiovascular function and alert the use of patients with seizures.

Behavioral problems in individuals that are often experienced by patients such as anxiety, behavioral problems, mood swings, irritability and agitation can be overcome with a psychosocial approach from the environment, family support, caregiver support and other professionals who can optimally, reduce the need for pharmacological drug use.[48] However, if not resolved, the use of psychotropic drugs is given as a last resort therapy if there are clear psychotic symptoms such as delusions, paranoia and hallucinations.[48] Antipsychotic treatment starts from giving 1 type of drug and the lowest effective dose possible, to minimize the side effects of the drug, most antipsychotic medications work by blocking dopamine receptors (D2) which interfere with dopaminergic transmission in the brain.[49]

Non-pharmacological therapy has begun to develop, in recent years, increasing interest in non-pharmacological interventions for patients is primely for patient psychology.[47] Multidimensional psychological approaches require positive support from various parties, especially families and caregivers.[47] However this psychological approach ensures that a great deal of responsibility rests with "system of care" in communicating effectively with patients, managing behavior, understanding attitude

changes, and dealing with the patient's emotional stress[50] Positive behavioral support from the family, a calm and safe environment should be beneficial for both the patient and the caregiver. This multidimensional interaction is useful for increasing patient independence, compensating for disability, increasing self-confidence and self-esteem, being able to adapt to the surrounding community and strengthening self-identity.[50]

2. Conclusion

People with DS present changes in the neuropathological lesions of AD over the age of 35 years. Individuals with DS have a significant chance of having AD. According to the amyloid cascade theory, the primary cause of the neuropathological characteristics associated with AD is the accumulation of amyloid (Ab) in the brain as well as the development of amyloid plaques which result in triplication of APP gene in DS individuals, as well as an extra copy of APP in familial AD patients. The two diseases are genetically related, considering the placement of amyloid precursors on chromosome 21. Overproduction of APP intermediate product, amyloid β (Aβ), and increasing its accumulation in the brain also accelerates downstream neurodegeneration, disturbs synapses signal, causes nerve cell death, tissue damage, and brain mass reduction at the end. People with DS who have AD will have problems in their memory function, social behavior, and cognition. Early detection of dementia-related DS is needed for early intervention and management, but AD-DS diagnosis is still challenging related to the absence of validated and standardised diagnostic instruments. Management of individuals with Down syndrome related to Alzheimer's disease is a holistic therapy that involves a multidisciplinary and multi-institutional approach from various professional fields including specialist doctors for monitoring therapy, psychologists for cognitive assessments, special nurses, psychiatrists and other professionals such as occupational therapists or speech and language therapists

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