Fall 2014

Early Onset Alzheimer's Disease in Individuals with Down Syndrome: Explored Theories of Pathophysiology

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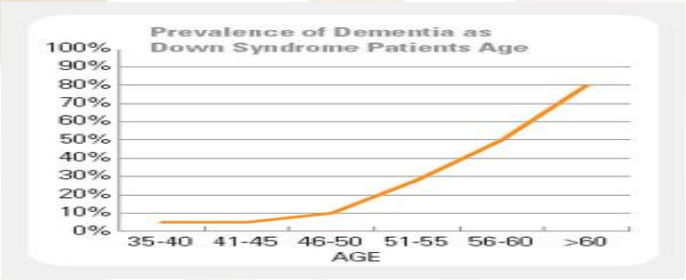
Introduction

This presentation is a focus on some of the theories of the pathophysiology of early-onset Alzheimer's Disease (AD) in individuals with Down Syndrome (DS). Down Syndrome, a genetic condition where an individual has a partial or full extra chromosome 21, is the most common chromosomal condition in the United States (National Down Syndrome Society (NDSS), 2012). Average life expectancy for individuals with DS has vastly increased in the last thirty years from age 25 to age 60 (NDSS, 2012). The extra chromosome genetically makes individuals with DS predisposed to certain conditions, including early onset dementia and AD, therefore as their life expectancy increases, so does their risk of developing this disease. Early-onset AD is characterized by having AD by the age 65. The purpose of this presentation is to aid practitioners in having a better understanding of the disease process in order to provide appropriate and timely diagnosis and treatment for this growing population.

Pathophysiological Processes

All individuals with DS, by the age of 40, will develop neuropathological changes of AD, including the hallmark signs of amyloid plaques and neurofibrillary tangles (NFTs) (Head et. Al, 2011). This neuropathological presentation has been attributed to the triplication and overexpression of the gene for amyloid precursor protein (APP), which is located on chromosome 21 (Jones et. al, 2011). This does not count for the entire picture, so other contributing factors must be explored.

Georgia Gwinnett, 2010.



Signs and Symptoms

Alzheimer's Association (2014) describes the early presentation of AD as difficulty in remembering newly learned information, with advances stages potentially presenting with mood or behavior changes, disorientation, more severe memory loss, and difficulty in walking, speaking, and swallowing. In individuals with DS, other symptoms of AD may appear first, especially behavior and mood changes. Ball, Holland, Watson and Huppert (2011) state that "preclinical stages of AD , as it develops in people with DS, are marked by changes in personality and behavior, associated with a specific impairment in the cognitive functions subserved by the frontal lobes" (p.321). Diagnosis in individuals with DS can also be difficult because the tasks performed in standard testing may not be possible for these individuals to perform. The Alzheimer's Association (2014) provides the following early symptoms of AD in individuals with DS:

- Reduced interest in being sociable, conversing or expressing thoughts
- Decreased enthusiasm for usual activities
- Decline in ability to pay attention
- Sadness, fearfulness or anxiety
- Irritability, uncooperativeness or aggression
- Restlessness or sleep disturbances
- Seizures that begin in adulthood
- Changes in coordination and walking
- Increased noisiness or excitability

Epidemiology

As previously discussed, all individuals with DS develop neuropathological changes of AD. Mean age of clinical diagnosis of AD in DS individuals is 51+/- 6 (Alvarez, Hoffmann, Hauser & Talavera 2014). A review of studies showed that 10-25% of patients had AD when aged 40-49 years, 20-50% had AD when aged 50-59 years, and 60-75% had AD when older than 60 years (Alvarez, Hoffmann, Hauser & Talavera, 2014)

Underlying Pathophysiology

AD is not completely understood, including in individuals with DS, however there are some known processes, including amyloid plaques and neurofibrillary tangles, and there are several additional theories to explain the processes of AD and early-onset AD beyond that. It is known that all individuals with DS have a partial or full triplication of chromosome 21, as well as amyloid plaques and NFTs by the age of 40. The following are examples of suggested theories to AD, AD in DS and early-onset AD:

- Head et al. (2011) state that the amyloid plaques contain the amyloid Beta peptide that is derived from a longer precursor protein, amyloid Beta protein precursor, the gene for which is on chromosome 21. Overexpression by triplication of this chromosome is suggested to be the cause of the excessive amyloid plaques in individuals with DS.
- Serano-Pozo, Frosch, Masliah, and Hyman (2011) state that neuropathological changes that occur in any AD include abundant amyloid plaques, neurofibrillary tangles along with neuropil threads, dystrophic neurites containing hyperphosphorylated tau that are accompanied by astroglials and microglial cell activation leading to the characteristic losses of neurons, nueropils, and synaptic elements. They also argue the neuroanatomical changes begin to accumulate ten years or more prior to the dementia diagnosis, making early detection of these changes important for early treatment.
- Jones, Margallo-Lana, Prasher, and Ballard (2008) suggest that the pathology consists of amyloid plaques, and NFTs with hyperphosphorylated tau in the form of paired helical elements. They state that a tetranucleotide repeat in intron 7 of APP has been associated with an earlier onset of dementia (Jones, Margallo-Lana, Prasher, and Ballard, 2008). The relevance of this to DS is that this is located on chromosome 21, which is triplicated in DS.
- Jones et al. do a later study that further discusses APP. The study states that APP is expressed in DS at levels four to five times higher than the general population (Jones et.al, 2011). They claim that the regulators of APP expression are also located on chromosome 21. The processing of APP results in production of beta amyloid which is deposited extracellularly in the brain, found as a core disease feature in people with AD (Jones et al., 2011).
- Wilcock and Griffin (2013) state that overexpression of APP and S100B and resultant overexpression of the pluripotent neuroinflammatory cytokine IL-1 end in multiple neural results that is characterized by gliosis-related neuroinflammation and the neuropathological changes of AD. S100B is an astrocyte-derived cytokine, encoded by chromosome 21 and is markedly elevated through life in individuals with DS.
- Ball, Holland, Watson and Huppert (2010) also explore the effects of SB100 in that it is involved in mediating growth of serotonin neurons. The study also revealed that individuals with DS who were on antidepressants was significantly associated with better performance in working memory tests.
- Coskun et al. (2010) proposed that etiology of premature dementia is the result of an underlying mitochondrial dysfunction resulting in energetic deficiency, increased oxidative stress, altered Calcium regulation, and predication to cell death through activation of mtPTP, resulting in a loss of neuronal process and neurons.

Significance of Pathophysiology

It is known that AD is partially a resultant of amyloid plaques and NFTs, and that individuals with DS will acquire both of these before the age of 40. Several studies have been done to suggest that there are other factors that play a role in early onset AD. It has been reported that early-onset AD in a general population is of the familial type, suggesting that the problem lies somewhere within genes. The significance of the pathophysiology in individuals with DS is that the triplication of chromosome 21 causes overexpression of proteins and other materials that lead to amyloid plaques and NFTs at an early age. The further study of individuals with DS can hold the key to answer questions that are still unanswered about the pathophysiology of early-onset AD and AD in general. Further studies could also explore the potential effects of selective serotonin reuptake inhibitors.

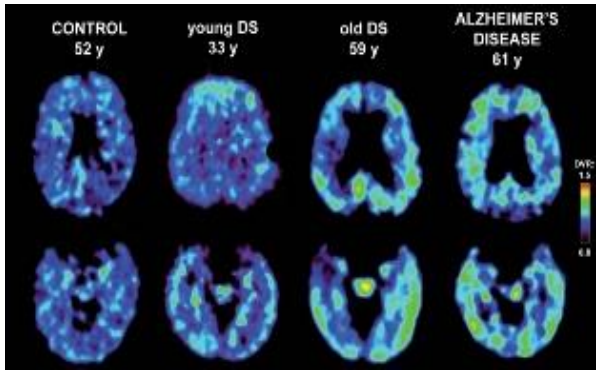
Implications for Nursing Care

Since it is known that all individuals with DS will have neuropathological features of AD, it is pertinent that health care professionals monitor for signs of cognitive change at an early age. A baseline cognitive and behavioral assessment should be performed on the DS individual by the age of 35 with an annual screening starting at age 40. Early signs of dementia and AD often go unnoticed in individuals with DS due to their atypical presentation of behavioral changes instead of memory impairment. Behavioral changes are also often attributed in the DS population as part of their developmental disability. Whitwan, McBrien, and Broom (2010) developed a standardized screening checklist to help health care professionals know when to make a referral for a dementia assessment for individuals with DS and other developmental disabilities.

Conclusion

Every individual with DS will have the AD hallmark diagnostic criteria of amyloid plaques and NFTs by the age of 40. The triplication of chromosome 21 that is characteristic of DS causes overxpression of genetic materials that contribute to this. This makes it evident that chromosome 21 is a primary factor that contributes to the development of AD. Further focused studies on the role that chromosome 21 plays in individuals with early onset AD can potentially be used to develop targeted drugs to stop of slow down the process.

Brain Scan Comparison of Individuals with DS and AD, Ghose, 2011.



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