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Neuroimaging and other modalities to assess Alzheimer's disease in Down syndrome☆

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ABSTRACT

People with Down syndrome (DS) develop Alzheimer's disease (AD) at higher rates and a younger age of onset compared to the general population. As the average lifespan of people with DS is increasing, AD is becoming an important health concern in this group. Neuroimaging is becoming an increasingly useful tool in understanding the pathogenesis of dementia development in relation to clinical symptoms. Furthermore, neuroimaging has the potential to play a role in AD diagnosis and monitoring of therapeutics. This review describes major recent findings from in vivo neuroimaging studies analysing DS and AD via ligand-based positron emission tomography (PET), [18F] fluorodeoxyglucose (FDG)-PET, structural magnetic resonance imaging (sMRI), and diffusion tensor imaging (DTI). Electroencephalography (EEG) and retinal imaging are also discussed as emerging modalities. The review is organized by neuroimaging method and assesses the relationship between cognitive decline and neuroimaging changes. We find that amyloid accumulation seen on PET occurs prior to dementia onset, possibly as a precursor to the atrophy and white matter changes seen in MRI studies. Future PET studies relating tau distribution to clinical symptoms will provide further insight into the role this protein plays in dementia development. Brain activity changes demonstrated by EEG and metabolic changes seen via FDG-PET may also follow predictable patterns that can help track dementia progression. Finally, newer approaches such as retinal imaging will hopefully overcome some of the limitations of neuroimaging and allow for detection of dementia at an earlier stage.

1. Introduction

Neuroimaging has important research and clinical implications in people with Down syndrome (DS) and Alzheimer's disease (AD). Correlating brain changes with clinical presentation can help uncover the mechanisms of dementia development. Clinically, neuroimaging of biomarkers can be used to track the development of AD in DS, allowing for deep phenotyping and analysis of therapeutic efficacy. Furthermore, neuroimaging can be used along with clinical symptoms to help confirm a diagnosis of AD in people with DS. After discussing relevant background information regarding DS and AD, this review provides an overview of clinical neuroimaging studies in the field from the past 10 years. The review is organized by in vivo neuroimaging methods, including ligand-based positron emission tomography (PET), [18F] fluorodeoxyglucose (FDG)-PET, structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), electroencephalography (EEG), and retinal imaging. Correlation of imaging changes to cognitive decline is considered, and a discussion of the limitations and feasibility of neuroimaging is included. This review is aimed at clinicians, psychologists, researchers, and those with an interest in DS and/or AD.

2. Background

2.1. Down syndrome overview

In order to appreciate the neuroimaging findings in people with DS

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; DS, Down syndrome; DTI, diffusion tensor imaging; EEG, electroencephalography; FDG, fluordexoyglucose; NFT, neurofibrillary tangles; PET, positron emission tomography; sMRI, structural magnetic resonance imaging

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and AD, it is important to understand the pathogenesis of DS and its link to AD. DS is a genetic abnormality resulting from an extra copy of chromosome 21, which manifests as intellectual disability and an array of physical characteristics. The vast majority of cases are due to a trisomy of chromosome 21, while 5% are due to Robertsonian Translocation or mosaicism (Wilson et al., 2014). This results in an increased dosage of the gene products on chromosome 21, which can disrupt a variety of pathways, including those involved with brain development, metabolism, and neuronal networks (Bouman and Hennekam, 2015). In regards to epidemiology, DS is one of the most common intellectual disabilities, occurring in 1/750 live births (Antonarakis et al., 2004). The risk of having a child with DS is linked to maternal age, with an 11/1000 chance in women over 40 (Puri and Morris, 2015). As our understanding of DS has increased, the lifespan of individuals with DS in developed countries has improved dramatically, as the average person with DS now lives into their 50s (Zigman and Lott, 2007). With this increase, it is important that we understand the aging process in DS and provide appropriate support throughout the lifespan.

2.2. Structural brain abnormalities in Down syndrome

Neurodevelopmental abnormalities in DS result in characteristic brain features. People with DS are brachycephalic and have a reduced overall brain size, with a specific reduction in the volume of the frontal and temporal lobes and the cerebellum (Newton, 2015). Within the temporal lobe, the superior temporal gyrus is reduced, while the parahippocampal gyrus can be increased compared to the general population. Recent findings (Lee et al., 2016) suggest that surface area reductions rather than a decrease in cortical thickness are responsible for the reduced cortical volume in certain areas. Furthermore, structural imaging findings (Annus et al., 2017) have found that the DS brain has a thicker frontal and occipitoparietal cortex, a thinner motor cortex and temporal pole, a smaller hippocampus and a larger putamen. Additionally, people with DS tend to show accelerated aging in their brains, demonstrating an adjusted brain-predicted age difference increase of 7.69 years (Cole et al., 2017). It has been demonstrated (Beacher et al., 2010) that the frontal, temporal and parietal lobes show greater age-related reduction than the general population. Understanding these structural differences is important in order to have a framework for how pathologies like dementia alter the DS brain.

2.3. Dementia and Down syndrome

AD is becoming an important health concern in people living longer with DS. People with DS are at an increased risk of developing dementia compared to the general population, and the onset occurs at a relatively younger age (Wilson et al., 2014). The prevalence of dementia in people with DS is about 3.4% in their 30s, 10.3% in their 40s, and 40% in those over 50 (Holland et al., 1998). Dementia can be difficult to diagnose in this population for a number of reasons. Individuals with DS may have a low baseline cognitive function, which can negatively affect their performance on cognitive tests designed for the general population that do not take into account the pre-existing intellectual deficits. People with DS also vary considerably in their intellectual ability, and this heterogeneity makes it difficult to establish reliable cut off scores on cognitive tests. For these reasons, DS-specific neuropsychological tests that take into account the spectrum of DS are needed in order to diagnose dementia in this population. In addition to the need for specialized cognitive tests, another challenge in diagnosis is that AD has a different initial presentation in DS compared to the general population, with changes in personality and executive function often manifesting before memory impairment (Wilson et al., 2014). One possible explanation for this is that the frontal lobe in DS is underdeveloped and thus more vulnerable to the effects of amyloid (Holland et al., 2000), but further research in this area is needed (Fonseca et al., 2016). An additional issue in diagnosing AD in people with DS is that they may struggle with communication, so there is often increased reliance on informant reports for diagnosis. Finally, DS is often associated with sensory, neurologic and psychiatric comorbidities which complicate the diagnosis of AD (Newton et al., 2015). For all these reasons, neuroimaging may be helpful as a complementary method of establishing a diagnosis and monitoring AD in this population.

2.4. Pathogenesis: The amyloid cascade hypothesis and other potential mechanisms

The amyloid cascade hypothesis is a major theory for the development of AD. Amyloid beta (Aβ) is a product of one of the pathways of amyloid precursor protein (APP) proteolysis, where APP is cleaved by beta-secretase 1 and gamma-secretase (Querfurth and LaFerla, 2010). Aβ peptides can vary slightly in length, and the Aβ42 form is particularly prone to aggregation, arranging into beta sheets that are responsible for amyloid plaques (Yan and Wang, 2007). In addition to the fibrillar form, there are also oligomer forms of Aβ42 that may have an even greater detrimental impact on neurons (Wilson et al., 2014). The risk of AD is higher in people with DS compared to people with non-DS intellectual disabilities (Strydom et al., 2013), and this is thought to be due to the presence of APP on human chromosome 21 (Goldgaber et al., 1987). The trisomy of chromosome 21 in people with DS therefore leads to increased dosage of APP and accumulation of insoluble, neurotoxic Aβ peptides.

Another biomarker for AD is tau, which correlates more closely with cognitive decline (Wolfe, 2009). Tau is a protein that allows for axonal transport of vesicles and organelles by associating with microtubules (Wilson et al., 2014). In AD, tau can no longer associate with microtubules because it is hyperphosphorylated and, as a result, neurotoxic neurofibrillary tangles (NFTs) are formed. Dual-specificity tyrosine-phosphorylation-regulated kinase 1A is located on chromosome 21, and excess of this kinase in DS could contribute to higher levels of hyperphosphorylated neurotoxic tau (Liu et al., 2008). On the other hand, animal studies suggest that Aβ pathology drives tau pathology, providing support for the amyloid cascade hypothesis as the key mechanism of AD in DS (Götz et al., 2001). On a molecular level, some findings suggest that amyloid influences the hyperphosphorylation of tau, promoting the presence of this neurotoxic form (De Felice et al., 2008). Regardless of the principle mechanism of tau pathogenesis, tau clearly plays a key role in neuronal degeneration.

An additional proposed mechanism in AD development is neuroinflammation. Amyloid plaques cause recruitment of microglia and interact with receptors on these cells, leading to production of pro-inflammatory cytokines and reactive oxygen species that are thought to be neurotoxic (Zotova et al., 2010). Because this is a downstream effect of amyloid, involvement of neuroinflammation is consistent with the amyloid cascade hypothesis of AD in DS. However, there is evidence of people with DS showing increased baseline expression of IL-1, an inflammatory cytokine, and chromosome 21 gene product S100B, a protein that is elevated in reactive astrocytes (Wilcock and Griffin, 2013). This suggests that neuroinflammation may also be working in parallel with the amyloid cascade to increase predisposition to AD.

In addition to these major theories, there are other genes on chromosome 21 that could play a role in premature brain aging, such as SOD-1 and SLC5A3 (Beacher et al., 2010). Mitochondrial dysfunction in neurons and astrocytes could also be involved, either independently or via altered metabolism of APP (Busciglio et al., 2002; Tiano and Busciglio, 2011). In sum, there are likely several mechanisms happening simultaneously to contribute to AD development in people with DS, but the amyloid cascade hypothesis is the most widely accepted theory for this population. While not all with DS eventually develop AD, these genetic factors certainly place them at risk.