Down syndrome and Alzheimer’s disease are two diseases you would not commonly associate. But Dr Elizabeth Head and Dr Frederick Schmitt, of the Sanders-Brown Center on Aging, have dedicated their research to identifying the key physiological and behavioural changes associated with Alzheimer’s disease onset in people with Down syndrome. They now plan on using this knowledge to support development of dementia-preventative treatments for people with Down syndrome.

Down syndrome accelerates Alzheimer’s disease onset

Down syndrome (DS) impacts approximately 60,000 people in the UK and 400,000 people in the United States. In 94% of cases, DS is a genetic disorder caused by a random triplication of chromosome 21. Intellectual disability, delayed growth, muscular weakness and distinctive facial features are the main characteristics but, with the appropriate education and support, people with DS can develop employable skills and live independent, rewarding lives. Often, people with DS have health problems due to their condition: approximately 50% of children born with DS may have congenital heart disease (CHD), more than 60% are visually impaired and many may also experience hearing loss, immune system deficiency, blood disorders and seizures. With careful monitoring, most of these conditions can be treated and, as a result, average life expectancy has increased to over 60 years. However, people with DS are at greater risk of developing age-related conditions such as Alzheimer’s disease (AD).

ALZHEIMER’S RISK
AD results from progressive brain degeneration, due to the formation of harmful ‘plaques’ and ‘neurofibrillary tangles’. These protein abnormalities block neuron connections, eventually leading to neuron death and brain tissue loss. Ultimately, long-term brain deterioration stimulates dementia onset, which involves symptoms such as memory loss, personality changes, problems with language and confusion. This debilitating condition increases in severity over time and, as it has no cure, people with AD often require constant care.

Interestingly, by the age of 40, virtually all people with DS have AD-associated brain changes. However, dementia symptom onset is often more variable. Clinical AD symptoms generally emerge approximately a decade after their brain tissue changes, generally when people are in their 50s or 60s. By exploring the neuropathological, cognitive and functional decline of people with DS, Drs Head and Schmitt aim to identify potential clinical targets, thus potentially preventing the development of dementia in older people with DS.

THE IMPACT OF CHROMOSOME 21 OVER-EXPRESSION
Genes on chromosome 21 are over-expressed, due to the chromosome’s triplication. This includes a key gene involved in AD development which encodes beta-amyloid precursor protein (APP). Cleavage of APP by two enzymes, β-secretase and γ-secretase, leads to beta-amyloid (Aβ) formation. Aggregations of these misfolded Aβ peptides become surrounded by fragmented neurons to

Magnetic resonance imaging (MRI) pictures showing the brain of an older person with Down syndrome (left) compared with a person of similar age without Down syndrome (right). Notice that the hippocampus, an area important for Alzheimer disease, is shrunk in Down syndrome.
produce senile plaques – an AD diagnostic hallmark. In fact, it has been shown that Aβ accumulation in plaques rapidly increases between the ages of 30 and 40 years in DS adults.

Furthermore, Aβ plaque deposition can indirectly increase brain oxidative stress. Oxidative damage is greater in people with DS compared to the general population. This is because in excessive quantities, Aβ peptides can damage mitochondria which can reduce the brain cells’ ability to maintain antioxidant defences. This consequently results in an inadvertent increase in reactive oxygen species (ROS) levels. The consequences of this oxidative stress are severe and include further mitochondrial damage and β-secretase expression. Ultimately, this creates a degenerative ‘ripple effect’, and DS individuals show an age-related increase in oxidised DNA/RNA.

Neurodegeneration, caused by another chromosome 21-located gene, such as DYRK1A, greatly accelerates AD progression in middle-aged DS adults. ‘Dual-specificity tyrosine phosphorylation-regulated kinase’ (DYRK1A) is an enzyme that contributes to hyperphosphorylation of the tau protein (a highly abundant neuronal microtubule stabiliser). This is extremely damaging as phosphorylated tau proteins become insoluble and aggregate, causing neurofibrillary tangle formation and neuron death. Previous research also indicates that phosphorylated tau levels greatly increase with age in DS adults.

CURRENT RESEARCH

The Down syndrome and Aging research team at the University of Kentucky are currently conducting a 10-year longitudinal study to explore aspects of cognitive decline associated with early-onset AD in people with DS. A range of magnetic resonance imaging (MRI) methods will be used by Drs Powell and Gold at the University of Kentucky to study: i) changes in white matter (WM) connections, ii) cerebrovascular dysfunction and iii) neuroinflammation.

Not only will the team continue to examine a cohort of older adults with DS (who have been volunteers for over six years), but they will also recruit a younger group of people with DS 25 years and older. This should enable the identification of the exact physiological, biochemical and behavioural processes that occur as AD develops.

Past research has shown that these factors are intertwined and are associated with AD onset in DS adults. For example, WM located in the frontal cortex degenerates as Aβ accumulates. Diffuse tensor imaging (DTI) is used to examine changes in WM integrity. DTI is a non-invasive, in vivo technique that measures the rate and direction of water molecule diffusion in the neural tissue. This reveals the architecture of WM and integrity loss in brain circuit connections can be observed over time.

Additionally, Aβ can build up on the blood vessels in the brain and can lead to cerebrovascular damage, and further WMD degradation. In fact, Aβ deposition occurs decades earlier in DS adults, compared to people without DS. To address the hypothesis that cerebrovascular damage increases the risk of dementia onset, MRI technology (arterial spin labelling used by Dr Ai-Ling Lin at the University of Kentucky) is being used to detect blood flow changes, cerebrovascular damage, and their progression in the volunteers with DS. Neuron inflammation is another key characteristic of AD. Aβ plaques bind to cell surface receptors on microglia (brain immune defence cells), triggering chemokine and cytokine release (chemicals which destroy plaques and damaged cells). However, some debatable evidence suggests that this immune response can actually accelerate the onset of AD. By studying the relationship between neuroinflammation and age, AD neuropathology and cognitive decline, Drs Head and Schmitt aim to tackle this important question by using blood biomarkers and magnetic resonance spectroscopy (chemical signals from brain).

THE UPSIDE OF DOWN SYNDROME

Overall, it is extremely important that we recognise AD development early on in people with DS, to assist patients and families.

This team’s initial research has already shown that as people with DS start to develop dementia several key changes occur in brain connectivity – which could act as early indicators. At the same time, clinical dementia diagnosis relies on obvious differences that friends and family can identify – namely changes in personality, behaviour, memory and learning and gait (i.e., slowing or hesitation in movement with age could indicate dementia onset).

Ultimately, the earlier these changes are detected, the easier preventative treatments (once developed) can be implemented to reduce AD dysfunction, drastically improving the quality of life of people with DS.

Q&A

Why are Down syndrome (DS) patients predisposed to age-related conditions such as Alzheimer’s disease (AD)?

Most of this is related to the changes in brain inflammation and cerebrovascular dysfunction and how they might contribute to the cognitive and behavioural traits associated with Alzheimer’s disease in Down syndrome. The aim of their work is to identify the earliest indicators of cognitive decline and develop preventative approaches that can reduce Alzheimer’s disease prevalence.

Where do you see your research focus in five years’ time?

I hope that we will have identified some of the key changes in cognition that are linked to brain pathology. We also hope that we can learn what age changes happen (e.g., when does cerebrovascular pathology start, when does inflammation start?) so that in future, when we develop clinical trials we will know not only what to change, but also when to change it.

It is extremely important we recognise Alzheimer’s disease development early on in Down syndrome patients, to predict who is vulnerable to dementia.