Alzheimer's disease associated with Down Syndrome: a Genetic form of Dementia

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Key points

- People with Down syndrome have an extra copy of chromosome 21
- A cross sectional study conducted to compare amyloid burden in individuals with Down syndrome versus in those with Alzheimer's disease
- Early amyloid dysregulation in people with Down syndrome

In order to discuss the diseases associated with Down syndrome, it is very crucial to understand what Down syndrome is and what its symptoms are. Down syndrome is a state or condition in which a person has an extra chromosome or an extra piece of a chromosome. This extra copy changes how a baby's body and brain develop and works. It can cause both mental and physical challenges during their lifetime. Even though people with Down syndrome might act and look similar, each person has different abilities and specialities.1

What causes Down syndrome?

Chromosomes are tiny "packages" in your cells that contain your genes. Genes carry information, called DNA that controls what you look like and how your body works. People with Down syndrome have an extra copy of chromosome 21. In some cases, they may have an extra copy of part of the chromosome. Having an extra copy of a chromosome is called trisomy. So sometimes Down syndrome is also called trisomy 21.

Down syndrome is usually not inherited. It happens by chance, as an error when cells are dividing during early development of the fetus. It is not known for sure why Down syndrome occurs or how many different factors play a role. One factor that increases the risk of having a baby with Down syndrome is the age of the mother. Women aged 35 or older are more likely to have a baby with Down syndrome.

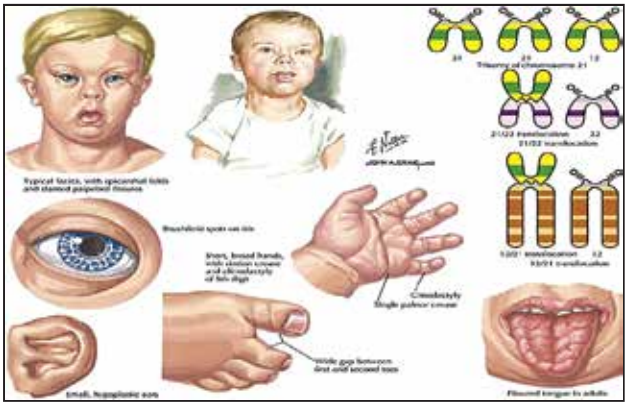

Fig 1: Comparison of amyloid burden in individuals with Down syndrome versus in autosomal dominant Alzheimer's disease

A cross sectional study was conducted to compare amyloid burden in individuals with Down syndrome versus in those with Alzheimer's disease. Important insights into the early pathogenesis of Alzheimer's disease can be provided by studies and investigations of autosomal dominant Alzheimer's disease and Down syndrome. However, it is not clear whether the timing and spatial distribution of amyloid accumulation differs between people with autosomal dominant Alzheimer's disease and those with Down syndrome. We aimed to compare directly the amyloid changes between these two groups of people.1

Adults with Down syndrome develop the neuropathological hallmarks of Alzheimer's disease and are at very great risk of developing early onset dementia, which is now the leading cause of death in this population. Diagnosis of dementia remains a clinical challenge because of the lack of validated diagnostic criteria in this population, and because symptoms are overshadowed by the intellectual disability associated with Down syndrome. In people with Down syndrome, fluid and imaging biomarkers have shown good and amazing diagnostic performances and a strikingly similar temporality of changes with respect to sporadic and autosomal dominant Alzheimer's disease. Most importantly, there are no treatments to prevent Alzheimer's disease, even though adults with Down syndrome could be an optimal population in whom to conduct could be an optimal population in whom to conduct Alzheimer's disease prevention trials. Unprecedented research activity in Down syndrome is rapidly changing this bleak scenario that will translate into disease-modifying therapies that could benefit other populations.2

Methods

In this cross-sectional study, we included participants or individuals (aged ≥25 years) with Down syndrome and sibling controls who had MRI and amyloid PET scans in the first data release (January, 2020) of the Alzheimer's Biomarker ConsortiumDown Syndrome (ABC-DS) study. We also included carriers of autosomal dominant Alzheimer's disease genetic mutations and non-carrier familial controls who were within a similar age range to

ABC-DS participants (25–73 years) and had MRI and amyloid PET scans at the date freeze time (December, 2020) of the Dominantly Inherited Alzheimer Network (DIAN) study. Controls from the two studies were merged into a single group. All DIAN study participants had genetic testing to determine PSEN1, PSEN2, or APP mutation status. APOE genotype was determined from blood samples. CSF samples were collected in a subset of ABC-DS and DIAN participants and the ratio of amyloid β42 (Aβ42) to Aβ40 (Aβ42/40) was measured to evaluate its Spearman's correlation with amyloid PET. Global PET amyloid burden was compared with regards to cognitive status, APOE 4 status, sex, age, and estimated years to symptom onset. We further analysed amyloid PET deposition by autosomal dominant mutation type. We also assessed regional patterns of amyloid accumulation by estimated number of years to symptom onset. Within a subset of participants the relationship between amyloid PET and CSF Aβ42/40 was evaluated.1

Interpretation:

Despite minor differences, amyloid PET changes were similar between people with autosomal dominant Alzheimer's disease versus Down syndrome and strongly supported early amyloid dysregulation in people with Down syndrome. Individuals with Down syndrome aged at least 35 years might take advantage from early intervention and warrant future inclusion in clinical trials, particularly given the relatively high incidence of Down syndrome.1

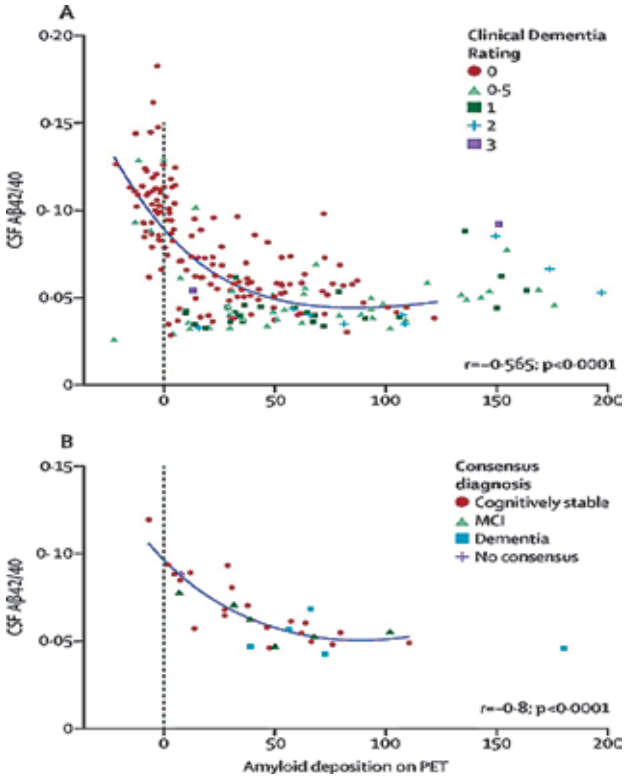

Fig 2: (Source; thelancet.com)

Association between Down syndrome and autosomal dominant Alzheimer's disease:

Down syndrome and autosomal dominant Alzheimer's disease are genetically determined forms of dementia according to researchers. Three causative genes associated with autosomal dominant Alzheimer's disease implicate amyloid β (Aβ) as a key player in disease pathogenesis: PSEN1, PSEN2, and APP. Similarly, Alzheimer's disease in people with Down syndrome is primarily driven and enhanced by the dose effect of having an extra copy of the APP gene, which is coded in the triplicated chromosome 21. These conditions, therefore, with their near-full penetrance, offer important opportunities to study the pathophysiology of Alzheimer's disease and to conduct prevention trials. Indeed, investigations of these conditions have provided some of the strongest and unique evidence for the amyloid cascade hypothesis.

Cognitive outcome measures for tracking Alzheimer's disease in Down syndrome

Down syndrome (DS) is now viewed or considered as a genetic type of Alzheimer's disease (AD), given the near-universal presence of AD pathology in middle adulthood and the elevated risk for developing clinical AD in DS. As the field of DS prepares for AD clinical intervention trials, there is a great need to identify cognitive measures which are specific and sensitive to the transition from being cognitively stable to the prodromal (e.g., Mild Cognitive Impairment—Down syndrome) and Most adults having Down syndrome do not self-report concerns about memory. Diagnosing Alzheimer's disease in a person with Down syndrome can be hard enough because of the challenges involved in assessing thinking-skill changes in persons with intellectual disabilities. Due to this reason, information from a caregiver or close family member can be especially helpful for the health care provider during the diagnostic process. Caregivers, for example, can check for changes in day-to-day function.1

References

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