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Biomarkers show value of studying dementia in Down syndrome

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Abstract

More than 90% of people with Down syndrome develop Alzheimer disease but receive little or no treatment for their dementia. Novel biomarkers of ageing and dementia bring new hope to this medically vulnerable population and can also help researchers understand dementia in other populations.

The average lifespan of people with Down syndrome (DS) has increased by more than threefold in the past 60 years[1], mostly owing to advances in medical care and higher overall levels of health. However, this longer lifespan comes with an increased risk of developing Alzheimer disease (AD). Trisomy of chromosome 21, which causes DS, results in an extra copy of *APP*; this gene encodes the amyloid-β precursor protein (APP), which is cleaved to produce amyloid-β (Aβ), and is associated with AD. The trisomy also results in additional copies of other AD-related genes that are involved in inflammation, redox metabolism and mitochondrial dysfunction[2]. Consequently, the lifetime risk of AD for adults with DS is >90%[3]. However, clinical diagnosis of dementia in adults with DS is challenging because the age of onset and the clinical symptoms are hetero geneous, in part owing to the variability in baseline functionality and differences in the severity of intellectual disability.

Imaging techniques, such as PET, have improved our understanding of the neuropathological processes that lead to DS-AD, but these techniques remain expensive and can be challenging to implement in vulnerable populations, such as those with DS. Fluid biomarkers have, therefore, become increasingly sought after and could shed light on disease progression in adults with DS compared with that in people with other genetic or sporadic forms of AD. Three new studies have demonstrated the utility of various biomarker methods, and the findings provide additional insight into the value of the population with DS for the study of AD in the general population.

In the first of these studies, Fagan et al.[4] compared patterns of cerebrospinal fluid (CSF) biomarkers in people with DS with those in carriers of autosomal dominant variants of AD; altered processing or overproduction of APP have been proposed as

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Competing interests

The authors declare no competing interests.

the main cause of AD in these two groups. The study was cross-sectional and included adults aged 30–61 years. CSF samples from adults with DS were obtained via the Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) in the USA, and samples from patients with autosomal dominant AD-associated mutations were collected through the Dominantly Inherited Alzheimer Network (DIAN) study. The biomarkers measured were the core AD biomarkers ($A\beta_{40}$, $A\beta_{42}$ and phosphorylated tau $(p\text{-}tau)_{181}$), a biomarker of neuroinflammation (YKL-40) and biomarkers of neuronal, axonal and synaptic injury (neurofilament light chain (NfL), tau, VLP1 and SNAP25).

The patterns of these CSF biomarkers were remarkably similar between adults with DS and carriers of autosomal dominant AD-associated mutations[4]. Adults with DS had higher absolute levels of $A\beta_{40}$ and $A\beta_{42}$ in the CSF than did mutation carriers, but the decrease in the $A\beta_{42}$:$A\beta_{40}$ ratio over time that is associated with progression of clinical symptoms was comparable between the two groups, suggesting that the timing of aggregation is similar. CSF levels of tau and NfL were already elevated in the asymptomatic stage in both groups, confirming that neuronal injury had occurred before symptoms of dementia developed. Previous imaging studies have shown that pre-symptomatic atrophy occurs in different brain areas in these two groups[5,6].

> "plasma levels of NfL could inform the diagnosis and prognosis of pre-symptomatic AD in people with DS"

Interestingly, the $p\text{-}tau_{181}$:$A\beta_{42}$ ratio was lower in participants with DS than in mutation carriers, even though this ratio increased in parallel in both groups. This finding suggests that this ratio could be used to predict conversion to dementia in people with DS. People with DS also had higher levels of YKL-40 than mutation carriers in the asymptomatic and symptomatic stages of AD. Immune dysfunction in DS is substantial and complex[7], but differences in the inflammatory profiles associated with DS-AD and other genetic forms of AD remain to be investigated. Overall, the study by Fagan et al.[4] highlights the similarities in the pathophysiological progression of AD in these two groups that are at high risk of AD, thereby demonstrating the need for alternative biomarkers (for example, markers of inflammation, oxidative stress and altered metabolism) that could predict the onset of dementia in people with DS.

The second study investigated blood biomarkers, an area to which much effort is being devoted because venipuncture is less invasive and more adapted to the clinical setting than lumbar punctures, especially for people with intellectual disabilities. Previous work has shown that plasma levels of NfL have clinical utility as a biomarker of neuronal injury and neurodegeneration[8], and, in the new study, Carmona-Iragui et al.[9] conducted a multicentre longitudinal cohort study to validate the clinical utility of plasma NfL levels for the diagnosis of symptomatic AD in DS. The investigators analysed 608 samples collected at six different sites from adults with DS.

> "inclusion of people with DS in clinical trials … could be of benefit to all populations with dementia"

Participants whose AD advanced during the longitudinal assessments were classified as progressors and participants whose disease remained in the same diagnostic category

were classified as non-progressors. Annual changes in plasma concentrations of NfL differed drastically between different groups. The annual increase was only 3.8% among asymptomatic non-progressors but was 11.5% among asymptomatic progressors and 24% among symptomatic non-progressors. The findings suggest that longitudinal changes in plasma levels of NfL could inform the diagnosis and prognosis of pre-symptomatic AD in people with DS. Carmona-Iragui et al.[9] conclude that the finding supports longitudinal assessment of plasma NfL levels as a theragnostic marker for clinical trials with excellent performance. NfL levels are elevated in many other neurodegenerative conditions and after trauma[8], so specificity for DS-AD is low and measurement of NfL levels should therefore be used in combination with other imaging, CSF or blood biomarkers.

In the third study, Montal et al.[10] used a proton magnetic resonance spectroscopy technique for regional tracking of metabolites in the brain in vivo. They examined two metabolites — myo-inositol and *N*-acetylaspartate, which are markers of neuro inflammation and neuronal damage, respectively — at different disease stages of AD in 118 adult participants with DS. Levels of these metabolites differed substantially between adults with DS and euploid healthy controls as the disease progressed. This technique has the distinct advantage that measurements can easily be included in standard MRI procedures and the metabolite changes can be correlated with CSF biomarkers. These findings further highlight the necessity of a diverse collection of biomarker techniques for an accurate diagnosis of DS-AD.

These recent studies have shown remarkable similarities in biomarkers as well as clini cal symptoms and brain pathology in AD in people with DS and people with other forms of genetic or sporadic AD. These findings suggest that the inclusion of people with DS in clinical trials of interventions for AD could be of benefit to all populations with dementia. Unfortunately, people with DS (>300,000 people in the USA alone and close to 6 million worldwide) have not traditionally been included in clinical trials for AD. The DS clinical trial networks that have formed in the past few years in Europe and in the USA should be commended for their engagement, and for their attempts to serve this historically under-represented group.

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