ALZHEIMER'S DISEASE IN DOWN SYNDROME. CSF, MRI, EEG AND PET MULTIMODAL STUDIES

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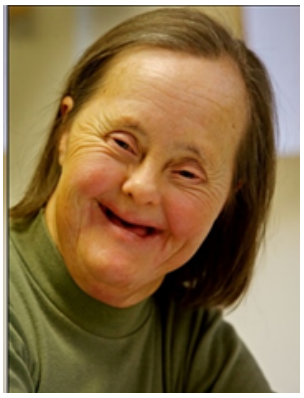
1. Summary of the project



Down syndrome (DS) is the major cause of intellectual disability of genetic origin in children, with an incidence of approximately 1 for every 650-1000 births (1). In 95% of cases, SD is caused by a complete trisomy of chromosome 21 (2). DS is associated with different comorbidities in the lifespan, but in adulthood, neurological diseases such as late-onset epilepsy and, especially, Alzheimer's disease (AD) are the most important (3). The cause of this strong association between DS and AD is due to the triplication in the amyloid precursor protein (APP) gene, encoded on chromosome 21. The triplication of APP is sufficient to cause autosomal dominant AD in those rare cases with triplication of this gene without trisomy. Moreover, the triplication of the APP gene in DS is necessary for the development of AD dementia. Indeed, DS cases with partial deletions which include the APP gene do not develop AD. In cases with full trisomy, at the age of 40, all people with DS present, at the neuropathological level, the neuropathological hallmarks of AD (neuritic plaques and neurofibrillary tangles) and the cumulative incidence AD exceeds 90% in the seventh decade of life. AD is, therefore, the main disease and cause of death among adults with DS (4).

The development of biomarkers in the last two decades has allowed a more accurate and earlier diagnosis of AD in the general population, and an unprecedented advance in the knowledge of its pathophysiology. However, there are very few studies of AD biomarkers in DS. These studies are, however, essential to disentangle the differences and similarities between sporadic AD and AD in DS, an essential knowledge in the development of future therapeutic strategies. Moreover, the study of AD biomarkers will enable more accurate diagnosis of AD in DS, a diagnostic challenge in this population due to the pre-existing intellectual disability associated with the syndrome.

The general aim of this project was the study of the natural history and the interrelations between the different AD biomarkers in DS. We studied the changes in brain structure with age as measured by cerebral magnetic resonance (MRI), the biochemical changes in cerebrospinal fluid (CSF) biomarkers of amyloid and tau, as well as the study of amyloid deposits and brain metabolism measured by positron

emission tomography (PET). We analyzed the impact these changes had on the cognitive trajectory in people with DS.

In order to carry out the project, we had the following objectives:

1) To compare people with DS with and without dementia through an analysis of cortical thickness in MRI, biomarkers of amyloidosis (BACE activity and levels of Aβ1-42 in CSF as well as florbetapir PET) and biomarkers of neuronal damage and inflammation in CSF (t-tau, p-tau and YKL-40), as well as FDG PET.
2) To analyze the relationship between the age of the subjects with DS and those same biomarkers.
3) To study the relationship between brain structure and metabolism and the biomarkers of amyloidosis and neuronal damage and inflammation in CSF.
4) To study the development of epilepsy in subjects with DS.
5) To study the relationship between neuropsychological performance and brain structure and metabolism as well as the biomarkers of amyloidosis and neuronal damage and inflammation in CSF.

2. Results

After obtaining this grant the project benefited from two FIS projects (PI14 / 01126 and PI17 / 01019 to Dr. Fortea), as well as a grant from La Caixa to Dr. Blesa and an R01 grant from the National Institute of Health (NIH) to Dr. Fortea. This additional funding has allowed us to increase the expected sample size.

Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) cohort

Since the beginning of the project (including the initial pilot phase) 332 adults with DS who have accepted at least one biomarker study have been clinically evaluated:

Biomarkers:

	Basal	Longitudinal
CSF	122	14
Plasma	332	96
MRI	135	22
Amyloid Florbetapir PET	60	-
Fluorodeoxyglucose PET	91	-
EEG	300	-
Polysomnography	60	-

This cohort now constitutes the largest cohort in the world of people with DS with multimodal AD biomarker studies. It has resulted in several publications in first decile journals and in numerous international collaborations.

Among the works with the potential to change current clinical practice in people with DS, we highlight two articles:

- The publication in the journal The Lancet Neurology in 2018 of the article entitled *"Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: a cross-sectional study"*. This study shows for the first time that CSF AD biomarkers are useful and reliable tools for the diagnosis of symptomatic AD in people with DS (*figure 1A).*It also shows that the determination of a new biomarker, the neurofilament light chain (NfL) levels in plasma, has the same diagnostic performance (*Figure 1C*). The discovery of a plasma biomarker with such good diagnostic performance can change the way we diagnose AD in people with DS due to its accessibility and relatively low cost. (*See Figure 1*).

- Another study with the potential to change clinical practice is the study entitled "*Prevalence of Sleep Disorders in Adults With Down Syndrome: A Comparative Study of Self-Reported, Actigraphic, and Polysomnographic Findings".* This polysomnographic study in adults with DS shows a very high prevalence of sleep apnea (OSA) which is not detected with the commonly used sleep quality questionnaires or sleepiness scales. Given the impact that OSA might have on cognition and morbimortality in this population, this study shows the importance of developing new population screening strategies for the detection and treatment of this treatable comorbidity.

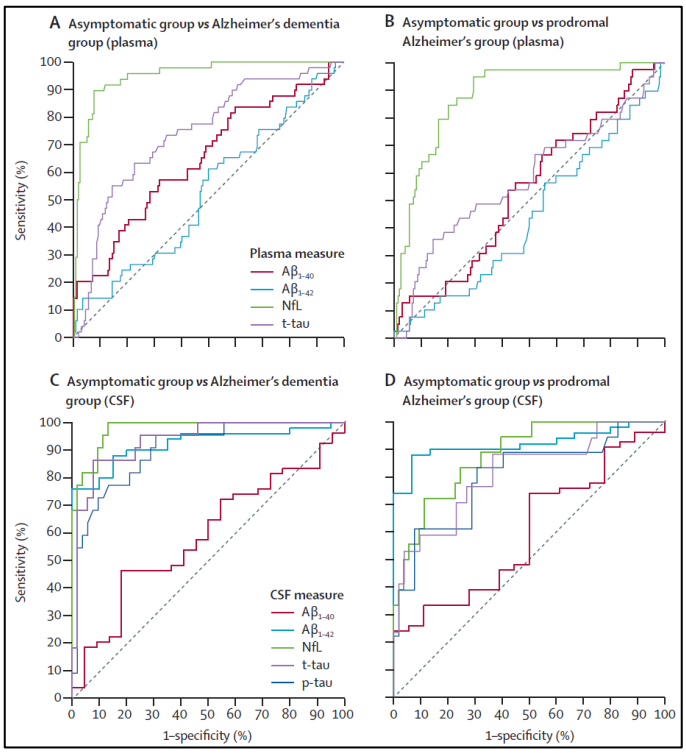


Figure 1: ROC curves showing the biomarkers diagnostic performance in plasma (A) and cerebrospinal fluid (C) when differentiating subjects with DS without cognitive impairment from those with established AD.

In addition to these studies, this project has led to other relevant publications that study the pathophysiology of AD in DS. In particular, we highlight three studies:

- The study *"Cerebral amyloid angiopathy in Down syndrome and autosomal-dominant Alzheimer's disease"* published in the journal Alzheimer and Dementia analyzed the cerebral amyloid angiopathy (CAA) in DS and compared it to that associated with sporadic and familial AD. This study showed that CAA is more frequent in DS and in familial AD than in sporadic AD, in agreement with the greater risk of cerebral hemorrhages in these populations. These results are relevant with respect to the

development of future treatments with anti-amyloid therapies, since most of the associated side effects are derived from the presence of CAA.

- We also highlight the studies *"Neuronal exosomes reveal Alzheimer's disease biomarkers in Down syndrome"* performed in collaboration with the University of Denver and the study *"Monoaminergic impairment in Down syndrome with Alzheimer's disease compared to early-onset Alzheimer's disease"* done in collaboration with the University of Groningen. Both works propose the use of new biomarkers to study of the pathophysiology of AD in DS. These studies also exemplify the great interest and the numerous international collaborations that the DABNI cohort has generated.

In addition to the aforementioned publications, other relevant works are in preparation. In this sense we highlight our preliminary neuroimaging results (*figure 2).*

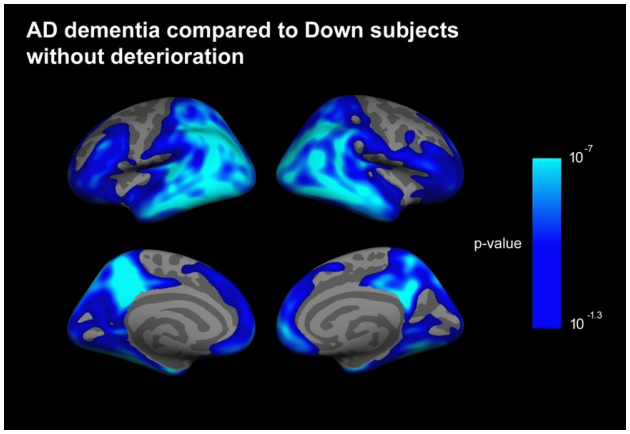


Figure 2: Cortical thickness study comparing subjects with DS without cognitive impairment and with established AD. The blue areas show the regions in which there is a cortical thinning, which correspond to those that are affected in typical AD.

The most important finding is that the areas vulnerable to AD in subjects with DS, both structurally and metabolically, overlap with those in sporadic AD. These findings are consistent with the early pathological which showed that the laminar intracortical and topographic distribution in the cortical mantle of amyloid deposition and tau pathology are identical to those found in sporadic AD. The relevance of these findings is that they support the use of DS as an exceptional biological model for the study of AD. In turn, these results confirm that the DS population can immediately benefit from the advances developed in the field of sporadic AD.

In summary, the project initiated thanks to this Fundació Marató TV3 grant has numerous strengths that make the DABNI cohort a unique initiative worldwide for the

study of AD in DS. Due to the additional funding obtained in this project, we can continue with the recruitment and prospective follow-up of this cohort, ensuring an extraordinarily promising future. This project is already improving the quality of life of adults with Down syndrome in Catalonia and is producing clinical evidence to change current clinical practice in DS and earlier and more accurate AD diagnosis in this population. Finally, DABNI is generating very numerous works and collaborations to advance in the knowledge the AD natural history in this population.

3. Generated literature

Scientific articles

1. Fortea J, Carmona-Iragui M, Benejam B, Fernández S, Videla L, Barroeta I, Alcolea D, Pegueroles J, Muñoz L, Belbin O, De Leon MJ, Maceski AM, Hirtz C, Clarimón J, Videla S, Delaby C, Lehmann S, Blesa R, Lleó A. Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet Neurol. 10/2018; 17(10):860-869. doi: 10.1016/S1474-4422(18)30285-0. IF: 27.138 WOS (JCR). Total citations at 18/01/19: 1 (WOS).

2. Giménez S, Videla L, Romero S, Benejam B, Clos S, Fernández S, Martínez M, Carmona-Iragui M, Antonijoan RM, Mayos M, Fortuna A, Peñacoba P, Plaza V, Osorio RS, Sharma RA, Bardés I, Rebillat AS, Lleó A, Blesa R, Videla S, Fortea J. Prevalence of Sleep Disorders in Adults With Down Syndrome: A Comparative Study of Self-Reported, Actigraphic, and Polysomnographic Findings. J Clin Sleep Med. 2018 Oct 15;14(10):1725-1733. doi: 10.5664/jcsm.7382.

3. Dekker AD, Sacco S, Carfi A, Benejam B, Vermeiren Y, Beugelsdijk G, Schippers M, Hassefras L, Eleveld J, Grefelman S, Fopma R, Bomer-Veenboer M, Boti M, Oosterling GDE, Scholten E, Tollenaere M, Checkley L, Strydom A, Van Goethem G, Onder G, Blesa R, Zu Eulenburg C, Coppus AMW, Rebillat AS, Fortea J, De Deyn PP. The Behavioral and Psychological Symptoms of Dementia in Down Syndrome (BPSD-DS) Scale: Comprehensive Assessment of Psychopathology in Down Syndrome. Journal of Alzheimer's Disease. 01/2018; 63(2): 797 - 819. doi: 10.3233/JAD-170920. IF: 3.476 WOS (JCR). Total citations at 18/01/19: 0 (WOS).

4. Dekker AD, Vermeiren Y, Carmona-Iragui M, Benejam B, Videla L, Gelpi E, Aerts T, Van Dam D, Fernández S, Lleó A, Videla S, Sieben A, Martin JJ; Netherlands Brain Bank, Blesa R, Fortea J, De Deyn PP. Monoaminergic impairment in Down syndrome with Alzheimer's disease compared to early-onset Alzheimer's disease. Alzheimers & Dementia. 11/2017; 10: 99 - 111. doi: 10.1016/j.dadm.2017.11.001. IF: 12.740 WOS (JCR). Total citations at 18/01/19: 0 (WOS).

5. Carmona-Iragui M, Balasa M, Benejam B, Alcolea D, Fernández S, Videla L, Sala I, Sánchez-Saudinós MB, Morenas-Rodriguez E, Ribosa-Nogué R, Illán-Gala I, Gonzalez-Ortiz S, Clarimón J, Schmitt F, Powell DK, Bosch B, Lladó A, Rafii MS, Head E, Molinuevo JL, Blesa R, Videla S, Lleó A, Sánchez-Valle R, Fortea J. Cerebral amyloid angiopathy in Down syndrome and sporadic and autosomal-dominant Alzheimer's disease. Alzheimers Dement. 11/2017; 13(11): 1251-1260. doi: 10.1016/j.jalz.2017.03.007. IF: 12.4, D1, WOS (JCR). Total citations at 18/01/19: 4 (WOS).

6. Hamlett E; Goetzl E; Ledreux A; Vasilevko V; Boger H; LaRosa A; Clarke D; Carroll S;Carmona-Iragui M; Fortea J; Mufson E; Sabbagh M; Mohammed A; Hartley D; Doran E; Lott I; Granhol AC. Neuronal exosomes reveal Alzheimer's disease biomarkers in Down syndrome. Alzheimers Dement. 05/2017; 13(5): 541-549. doi: 10.1016/j.jalz.2016.08.012. IF: 9.470, DI, WOS (JCR). Total citations at 18/01/19: 19 (WOS).

7. García-Ayllón MS, Lopez-Font I, Boix CP, Fortea J, Sánchez-Valle R, Lleó A, Molinuevo JL, Zetterberg H, Blennow K, Sáez-Valero. C-terminal fragments of the amyloid precursor protein in cerebrospinal fluid as potential biomarkers for Alzheimer disease. J. Sci Rep. 05/2017; 7(1):2477. doi: 10.1038/s41598-017-02841-7. IF: 9.129, source: web. Total citations at 18/01/19: 3 (WOS).

8. Kamer AR, Fortea JO, Videla S, Mayoral A, Janal M, Carmona-Iragui M, Benejam B, Craig RG, Saxena D, Corby P, Glodzik L, Annam KR, Robbins M, de Leon MJ. Periodontal disease's contribution to Alzheimer's disease progression in Down syndrome. Alzheimers Dement (Amst). 2016 Feb 4;2:49-57. doi: 10.1016/j.dadm.2016.01.001. eCollection 2016. Review. PMID: 27239536.

9. Carmona-Iragui M, Santos T, Videla S, Fernández S, Benejam B, Videla L, Alcolea D, Blennow K, Blesa R, Lleó A, Fortea. Feasibility of Lumbar Puncture in the Study of Cerebrospinal Fluid Biomarkers for Alzheimer's Disease in Subjects with Down Syndrome. J. J Alzheimers Dis. 2017;55(4):1489-1496. doi: 10.3233/JAD-160827. IF: 3.731, Q1, WOS (JCR). Total citations at 18/01/19: 2 (WOS).

Other publications

1. Chapter "Dementia and intellectual disability: DS" of the Spanish Society of Neurology Clinical Guide of dementias, November 2018.

2. Chapter "Alzheimer's disease and other neurological problems of the adult with Down syndrome" of the guide: Down syndrome, notebooks of good medical practice. Ahead of print.

Congress communications

This project has been presented in 9 national congresses (10 oral communications and 2 posters), 17 international congresses (23 communications, 2 posters) and in 9 invited papers.

Mentions in press

Medio	Fecha	Título	Soporte
Agencia EFE	30/08/ 2018	Logran detectar precozmente el Alzheimer en personas con Síndrome de Down	Prensa/ Internet
MSP (Medicina y Salud Pública)	30/08/ 2018	Biomarcador en sangre detecta el alzhéimer en personas con down	Prensa/ Internet
Saludiario.es	30/08/ 2018	Un biomarcador en sangre permite detectar la enfermedad de Alzheimer en personas con síndrome de Down	Pensa/ Internet
CatalunyaDiari	31/08/2018	Nou mètode per detectar precoçment l'Alzheimer en persones amb Síndrome de Down	Prensa/ Internet
Laverdad.es	30/08/2018	Un avance en la lucha contra el alzhéimer en personas con Down	Prensa/ Internet
NacióDigital	30/08/2018	Nou avenç per la detecció precoç de l'Alzheimer en persones amb síndrome de Down	Prensa/ Internet
Eropapress	30/08/2018	Un biomarcador en sangre detecta el Alzheimer en personas con síndrome de Down	Prensa/ Internet
Geriatricarea.com	6/09/2018	Un biomarcador en sangre detecta el Alzheimer en personas con síndrome de Down personas con síndrome de Down	Prensa/ Internet Internet
ABC	30/08/2018	Un análisis de sangre detecta el alzhéimer de forma precoz	Prensa/ Internet
El Periódico	30/08/2018	Avances en la detección del alzhéimer en personas con Síndrome de Down	Prensa/ Internet
RTVE	30/08/2018	Un biomarcador permite la detección precoz del alzhéimer en personas con síndrome de Down	Prensa/ Internet
CCA	30/08/2018	Detectar l'alzheimer en persones Down fins a 10 anys abans amb una anàlisi de sang	Prensa/ Internet
Ara.cat	30/08/2018	Un biomarcador en sang permet la detecció precoç de l'Alzheimer en persones amb síndrome de Down	Prensa/ Internet
El mundo	30/08/2018	Logran detectar precozmente el Alzheimer en personas con síndrome de Down	Prensa/ Internet
El Periódico	30/08/2018	Adelantarse al Alzhéimer	Prensa
La Vanguardia	30/08/2018	Un análisis detecta Alzheimer Precoz en los Down	Prensa
Cadena SER	30/08/2018	Una analítica permet detectar l'Alzheimer precoç en els Down	Prensa/ Internet
TV3	30/08/2018	Nova anàlisi per diagnosticar l'Alzheimer	TV
Telemadrid	30/08/2018	Logran detectar precozmente el Alzheimer en personas con Síndrome de Down	TV
RTVE	30/08/2018	Un biomarcador en sang permet la detecció precoç de l'Alzheimer en persones amb síndrome de Down	TV

Awards and honors

"Alzheimer 2017 Award" by the Spanish Society of Neurology. The prize is awarded to the Fundación Catalana SD in recognition of its dual work, both scientific and research as well as social and informative for patients with DS and Alzheimer's and their families. Presentation: June 7, 2018 at the headquarters of the Spanish Society of Neurology

References

1. Bittles A.H. et al. Eur. J. Public Health 17, 221–5 (2007).
2. Antonarakis S.E. et al. N. Engl. J. Med. 324, 872–876 (1991).
3. Lott I.T. et al. Lancet Neurol. 9, 623–33 (2010).
4. Hithersay R. et al. JAMA Neurol. (2019: ahead of print)