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POSTER N.º 1

Introduced by: López Torres, Isabel

Title:

SCAP-AD: RESEARCH PROJECT FOR THE EARLY DETECTION OF ALZHEIMER'S DISEASE

Principal Investigator: Isabel López-Torres

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Abstract:
"Objectives Alzheimer's disease (AD) is the most common neurodegenerative disease (60-80% of dementias) that seriously impacts the lives of many patients and their families. There are no curative treatments for AD, but in recent years new drugs are being developed that could modify its course. To apply these new therapies, it is necessary to make an early and accurate diagnosis of the disease. The SCAP-AD project aims to validate precision medicine tools to identify preclinical Alzheimer's disease. Material and Methods The SCAP-AD is a multicenter project, coordinated by CIEN, involving 13 Spanish research centers. Two large cohorts of subjects over 60 years of age, without a diagnosis of dementia will be recruited: a digital cohort (n=50,000) where the use of digital biomarkers through a web platform will be explored, and a clinical validation cohort (n=1,000) in which clinical, neuroimaging, plasma and cerebrospinal fluid markers studies will be performed. Results The main goal of the project is to improve the prevention and diagnosis of AD by integrating precision medicine tools to create strategies to identify the disease in its early preclinical and clinical stages. Conclusions This project is funded by the Instituto de Salud Carlos III (ISCIII) under the European NextGenEu funds that finance the actions of the Recovery and Resilience Mechanism and has the approval of its Research Ethics Committee. Keywords: Alzheimer's disease, precision medicine, biomarkers, early detection.

POSTER N.º 2

Introduced by: Uceda-Heras, Alicia

Title:

GFAP STAINING ALONG THE MEDIAL TEMPORAL LOBE IN HUMAN POSTMORTEM BRAIN TISSUE OF PATIENTS FROM THE VARS DEMENTIA COHORT

Principal Investigator: Alicia Uceda-Heras

Authors: Alicia Uceda-Heras, Iván Burgueño-García, Laura Saiz-Aúz, Paloma Ruiz-Valderrey, María José López-Martínez, Alberto Rábano

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Abstract:
“GFAP labels activated astrocytes and has been proposed as biomarker of Alzheimer’s disease (AD). GFAP was recently analyzed with findings that demonstrated an association between serum GFAP levels and post-mortem tau pathology. Now, we have studied the histological detection of GFAP in association with neuropathological variables. We analyzed 154 donated brains from the Vallecas Alzheimer’s Reina Sofía (VARS) cohort. We developed immunohistochemistry assays for GFAP in entorhinal cortex (EC) and amygdala (A) and measured the area stained with GFAP antibody through Cell-Profiler program. We observed that the extension of GFAP marker is higher in the superficial layers of EC as compared to the deep layers, therefore, we continued the analysis restricted to superficial layers of EC and the basolateral nuclei of A. We found a correlation ($r=0.173$; $P<0.05$) between GFAP in EC and Braak tau stages, and a correlation ($r=0.189$; $P<0.05$) of GFAP in A with LPC classification. Regarding EC, we observed a trend of increasing GFAP staining with higher stages of Braak tau, NIA B, Thal stage, NIA A, Nia C, HS (stages 0-4) and TDP-43 stage (Josephs et al). Finally, with respect to copathologies, we noted that in both structures, A ($P<0.05$) and EC ($P<0.01$), GFAP staining is higher in presence of 3-4 copathologies with middle/high burden of the pathology as compared with <2 copathologies. These findings altogether support the role of GFAP as AD biomarker, and as a possible marker of copathologies. The prospects for the study are to compare plasma levels of GFAP with histological data.

POSTER N.º 3

Introduced by: Vicario Abejón, Carlos

Title:

HUMAN APOE POLYMORPHISM IS INVOLVED IN THE MORPHOLOGICAL AND FUNCTIONAL CHANGES OF IPSC-DERIVED ASTROCYTES FROM ALZHEIMER'S PATIENTS DURING INFLAMMATION

Principal Investigator: Rebeca Vecino

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Abstract:
"Alzheimer´s disease (AD) is the leading cause of dementia in the aging population, with the ε4 allele of apolipoprotein E (APOE) being the strongest genetic risk factor. Astrocytes mediate key processes during AD progression, such as the clearance of amyloid-beta aggregates and the inflammatory response. However, the impact of different APOE alleles during astrocyte development, maturation, and function remains to be fully understood. Here, we obtained induced pluripotent stem cells (iPSCs) from fibroblasts of AD patients carrying ε3 and ε4 alleles (in homozygosis) and from healthy individuals. We also used gene-edited iPSC lines homozygous for the main APOE variants and an APOE knock-out line. Human astrocytes were generated by establishing a differentiation protocol by adding small molecules and growth factors. Then, the expression of typical markers and APOE was analyzed to confirm its astrocytic phenotype. In addition, astrocytes exhibited calcium wave production and glutamate uptake capacity. They also responded to an inflammatory stimulus or the presence of Aβ by increasing the expression levels and release of proinflammatory cytokines (such as IL-6) and changing their morphology. Our results show that APOE polymorphism affects the basal state of astrocytes and their capacity to react to both stimuli by acquiring different morphologies. Furthermore, the ε4 allele could alter Aβ uptake/degradation capacity by astrocytes and its distribution within the cell. Our findings highlight the relevance of APOE polymorphism in the morphological and functional profile of astrocytes and their potential correlation with the risk of developing AD."

POSTER N.º 4

Introduced by: Trujillo Estrada, Laura

Title:

MITOCHONDRIA ULTRASTRUCTURAL PATHOLOGY OF REACTIVE ASTROCYTES IN ALZHEIMER'S DISEASE

Principal Investigator: Elba Lopez-Oliva

Authors: Lopez-Oliva E1, Trujillo-Estrada L1, Fernandez-Valenzuela JJ1, Sanchez-Mejías E1, Mejias-Ortega M1, Vizuete M2, Vitorica J2 and Gutierrez A1

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Abstract:
"In Alzheimer's disease (AD) astrocytes become reactive participating in the inflammatory response and playing a key role in disease progression. However, there is a limited understanding of the changes in reactive astrocytes that might lead to a dysfunctional state contributing neuronal disturbances in AD. Astrocytes are the prevalent glial cells and have many functions aimed at maintaining brain homeostasis including regulation of brain energy metabolism and maintenance of the blood-brain barrier. AD is characterized by brain hypometabolism and mitochondrial dysfunction, and although most studies have focused on neurons little is known about the dysfunction of astrocytic mitochondria in this disorder. Here, we have performed an ultrastructural analysis of reactive astrocytes, using transmission electron microscopy combined with immunogold labeling and image analysis, in the hippocampus of amyloidogenic (APP/PS1) and tauopathy (P301S) transgenic mice (4, 6 and 12 months). Our results show remarkable morphological alterations in the reactive astrocytes mitochondria that include double membrane rupture, cristae loss and loss of their circularity. Since mitochondrial morphology is directly related to mitochondrial fusion/fission processes, the ultrastructural changes observed in astrocyte mitochondria suggest dynamic abnormalities in these organelles that may lead to deficits in astroglial function compromising their capability to maintain brain homeostasis. A better understanding of cell type-specific mitochondrial dysfunction might hold great potential for the exploration of novel molecular targets for future disease modifying therapies. Supported by PI21-0915(AG),PI21-00914(JV) from Instituto de Salud Carlos III co-financied by FEDER funds from European Union; Universidad de Málaga PPIT.UMA.B1-2021_32(LTE); Junta de Andalucia and CIBERNED (AG and JV).

POSTER N.º 5

Introduced by: Ricciardi Serra, Mario Emiliano

Title:

DETECTION OF CEREBRAL AMYLOID ANGIOPATHY (CAA) IN ALZHEIMER'S DISEASE (AD) USING BLOOD BIOMARKERS.

Principal Investigator: Mario Ricciardi

Authors: Mario Ricciardi | Elizabeth Valeriano-Lorenzo| María Ascensión Zea-Sevilla | Meritxell Valenti | Belén Frades | Alicia Ruiz-Gonzalez | Ana Belén Pastor | Francisco LópezGonzalez | Paloma Ruiz | Laura Saiz | Iván Burgueño-Garcií | María José López-Martinez | Alberto Rábano | Teodoro Del Ser | Pascual Sánchez-Juan

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Abstract:
"Background: The Amyloid-Related Imaging Abnormalities (ARIA) produced by anti-amyloid drugs and the clinical repercussions of the disease raise the need for earlier biomarkers than MRI in CAA. This research aims to evaluate in patients with pathologically confirmed AD the correlation between CAA severity, serum biomarker levels and APOE genotypes. Methods: Cases with a pathological diagnosis of AD according to NIA-AA criteria were selected. In each case, CAA was assessed according to the criteria of Vonsattel et al. (grade 0 to 3), APOE was genotyped, and serum levels of Ab40, Ab42, Tau-total, and p-Tau181 were determined using SIMOA. A descriptive, correlation (Spearman coefficient) and comparison (Mann-Whitney U test) analysis of the data were performed. Using a Kruskal-Wallis analysis, biomarker levels and APOE genotypes were compared among the 3 groups of CAA severity (grade 0-1, grade 2, and grade 3). Results: A total of 104 cases were included: 10 grade 0, 36 grade 1, 46 grade 2, and 12 grade 3 CAA. 97% had a high Braak stage (5 or 6). A higher grade of CAA correlated with lower levels of Ab40 (rs= -0.225, p= 0.02) and p-Tau181 (rs= -0.251, p= 0.01) and was associated with a higher frequency of APOEε4 (U= 865.5, z-score 3.20281, p= 0.00069). Ab40 levels showed an inverse gradient to the degree of CAA severity in the 3 groups (medians: 235 pg/mL, 212 pg/mL and 190 pg/mL), with a significant difference between groups (H= 6.407, p= 0.04). Conclusions: The severity of CAA is associated with decreasing serum levels of Ab40 and increased presence of APOEε4."

POSTER N.º 6

Introduced by: Oliveira, Cátia

Title:

ENCEPHALOPATHY WITH REVERSIBLE MULTIFOCAL CEREBRAL EDEMA: AN ATYPICAL PRESENTATION OF A NEURODEGENERATIVE DISEASE

Principal Investigator: Cátia Oliveira

Authors: Oliveira C. 1, Castro R. 1, Pires A. 1, Fontão L.1

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Abstract:
“Introduction: Cerebral amyloid angiopathy is an increasingly reported disorder in older people, although its inflammatory subtype (iCAA) is much rarer. It can present in several ways and its diagnosis may be challenging. Case Report: A 64-year-old woman with untreated hypertension and a history of treated low-grade urothelial carcinoma presented with progressive cognitive dysfunction, including language, memory, and visuospatial impairments, over the course of four weeks. No history of seizures or psychiatric symptoms was present. Examination revealed a blood pressure of 170/73 mmHg, attention deficits, and mixed aphasia. Brain imaging showed extensive bilateral cortico-subcortical edema, particularly in the frontal, temporoparietal, and occipital regions, brainstem, left hippocampus, and caudate nuclei, without contrast enhancement or vascular abnormalities. After aggressive blood pressure control and a course of corticosteroids (Methylprednisolone 1g for five days), the patient showed clinical and imaging improvement. Initial CSF analysis revealed hyperproteinorrachia, but all tests for neoplasms, systemic autoimmune disorders, and infections were negative. One year later, the patient continues to have slowly progressive memory and visuospatial dysfunction. Follow-up MRI showed complete resolution of the edema but the appearance of cortical microhemorrhages. The CSF analysis indicated low levels of beta-amyloid (1-42) and elevated phosphorylated tau. Conclusions: This case presents a striking clinical and imaging example of a reversible multifocal vasogenic brain edema. Initially, the differential diagnosis seemed to be primarily between atypical reversible posterior encephalopathy syndrome or iCAA, after exclusion of other neoplastic, autoimmune, and infectious causes. During follow-up, iCAA appears as the most likely diagnosis highlighting the importance of clinical suspicion of this condition.”

POSTER N.º 7

Introduced by: Sanchez-Mejías, Elisabeth

Title:

UNRAVELING THE PLAQUE-ASSOCIATED MYELOID CELL LANDSCAPE IN THE HUMAN ALZHEIMER'S BRAIN

Principal Investigator: Elisabeth Sanchez-Mejias

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Abstract:
Microglia are the resident innate immune myeloid cells of the brain and play a critical role in the pathological process of Alzheimer´s disease (AD) since genetic risk variants for late-onset AD are expressed exclusively or highly in these glial cells. Though the diversity of functional states of microglial cells in AD continuum is still unknown, loss of microglial neuroprotective and phagocytic function indicates the critical involvement of malfunctioning microglia in driving pathological progression and neurodegeneration. Moreover, little is known about the diversity of myeloid cells across different brain regions along the AD continuum. In this work, we have analyzed the responsive myeloid phenotype to amyloid pathology in two AD vulnerable brain regions, frontal cortex and hippocampus. For this purpose, immunolabeling for a wide range of markers combined with image analysis approaches have been carried out in postmortem samples from AD patients with dementia (Braak V-VI) and age-matched asymptomatic cases (Braak II). While the frontal cortex showed strong microglial activation around plaques, the hippocampus of the same individuals showed an exhausted microglial response including degenerative/senescent features. Regional differences were also found in the microglial phagocytic capacity. By counting the number of different microglial subsets, according to the combination of markers expressed, we found that the microglial composition of plaques was highly heterogeneous. Interestingly, even though some Braak II individuals presented high amyloid pathology, only AD patients exhibited infiltration of CD163 monocyte-derived cells that invaded plaque near blood vessels. These results reveal the co-existence of distinct myeloid populations associated with amyloid plaques during disease progression and open the opportunity to design targeted therapies, not only to microglia, but also to peripheral immune cell population to modulate amyloid pathology. Supported by ISCiii grants PI21/00915 (to AG) and PI21/000914 (to JV) co-financed by FEDER funds from European Union; and by CIBERNED

POSTER N.º 8

Introduced by: Sáez-Valero, Javier

Title:

RISK FOR SARS-COV2 BRAIN ENTRY THROUGH ACE2 AND TMPRSS2 IS NOT INCREASED IN ALZHEIMER'S DEMENTIA, BUT IT IS IN DOWN SYNDROME

Principal Investigator: Javier Sáez-Valero

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Abstract:
Many studies suggest an increased vulnerability of Alzheimer's disease (AD) patients and Down syndrome (DS) subjects to COVID-19; however, it is unclear whether it is derived from an increased risk of brain infection. The SARS-CoV-2 coronavirus infects cells through the angiotensin-converting enzyme 2 (ACE2), and the serine protease TMPRSS2 for the priming of viral spike (S) protein. ACE2 is cleaved from the plasma membrane through constitutive and regulated shedding, whereas TMPRSS2 undergoes autoproteolytic cleavage at the ectodomain to acquire proteolytic activity. For both proteins ectodomain fragments and soluble full-length forms co-exist in biological fluids, but different dynamics in species may overlap during disease progression, hindering the interpretation of changes. We have addressed whether ACE2 and TMPRSS2 are altered in AD and DS subjects regarding vulnerability to SARS-CoV-2 infection. ACE2 and TMPRSS2 are present in cerebrospinal fluid (CSF) including fragments and full-length forms. Increases in cleavage of membrane ACE2 and in CSF levels can be interpreted as protective for SARS-CoV-2 infection since soluble ACE2 can also bind the virus. In AD cases ACE2 full-length species decreased in CSF, mirroring the decrease in membrane resident ACE2. However, DS patients presented less proteolytic processing of ACE2. Regarding TMPRSS2, increases in the active fragment could reflect increased vulnerability to infection. In DS subjects, as expected due to the trisomy in the TMPRSS2 gene, full-length and fragments are increased in CSF. In conclusion, DS patients displayed changes in ACE2 and TMPRSS2 that determined increased vulnerability to SARS-CoV-2 brain infection, but this condition is not associated with proneness to develop AD.

POSTER N.º 9

Introduced by: Wolfram, Martin

Title:

CASCADE AUTOHYDROLYSIS OF ALZHEIMER'S AB PEPTIDES

Principal Investigator: Morten Meldal

Authors: "Martin Wolfram Manish K. Tiwari Tue Hassenkam Ming Li Morten J. Bjerrum Morten Meldal "

Filiation: Department of Chemistry, University of Copenhagen, Denmark.

Abstract:
Protein/peptide self-assembly into amyloid structures associates with major neurodegenerative disorders such as Alzheimer's disease (AD). Soluble assemblies (oligomers) of the Aβ peptide and their aggregates are perceived as neurotoxic species in AD. While screening for synthetic cleavage agents that could break down such aberrant assemblies through hydrolysis, we observed that the assemblies of Ab oligopeptides, containing the nucleation sequence Aβ14–24 (H14QKLVFFAEDV24), could act as cleavage agents by themselves. Autohydrolysis showed a common fragment fingerprint among various mutated Aβ14–24 oligopeptides, Aβ12–25-Gly and Aβ1–28, and full-length Aβ1–40/42, under physiologically relevant conditions. Primary endoproteolytic autocleavage at the Gln15–Lys16, Lys16–Leu17 and Phe19–Phe20 positions was followed by subsequent exopeptidase self- processing of the fragments. Control experiments with homologous D-amino acid enantiomers Aβ12–25-Gly and Aβ16–25-Gly showed the same autocleavage pattern under similar reaction conditions. The autohydrolytic cascade reaction (ACR) was resilient to a broad range of conditions (20–37 °C, 10–150 μM peptide concentration at pH 7.0–7.8). Evidently, assemblies of the primary autocleavage fragments acted as structural/compositional templates (autocatalysts) for self-propagating autohydrolytic processing at the Aβ16–21 nucleation site, showing the potential for cross-catalytic seeding of the ACR in larger Aβ isoforms (Aβ1–28 and Aβ1–40/42). This result may shed new light on Aβ behaviour in solution and might be useful in the development of intervention strategies to decompose or inhibit neurotoxic Aβ assemblies in AD.

POSTER N.º 10

Introduced by: Zhang, Linda

Title:

KLOTHO-VS HETEROZYGOSITY AMELIORATES THE EFFECTS OF APOE E4 ON LONGITUDINAL HIPPOCAMPAL ATROPHY

Principal Investigator: Linda Zhang

Authors: Linda Zhang1, Eva Alfayate1, Miguel Calero 2,3, Miguel Medina 2,3, Bryan Strange 1,4, Pascual Sanchez-Juan 1, and Michel J. Grothe 1

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Abstract:
“Background: KLOTHO-VS heterozygosity (KL-VShet+) has been posited to be a protective factor against age-related disease and cognitive decline, having been associated with increased cortical volumes and brain connectivity, as well as improved cognition in healthy elderly individuals. Conversely, the APOE-ε4 allele is a primary risk factor for the development of Alzheimer’s disease (AD), with ε4 carriers more likely to have greater β-amyloid burden, earlier age of AD onset, and accelerated rates of cognitive decline. Relatively few studies have investigated the interaction between these two genetic factors, with those that have presenting conflicting findings. Methods: 720 cognitively normal elderly participants with 3T T1-weighted MRI, APOE and KL-VS genotyping were selected for cross-sectional analyses from the Vallecas Project cohort, a single-centre 12-year longitudinal study with annual follow-ups. Of these participants, 443 had at least two visits and were included in longitudinal analyses (average follow-up 4.7 years). Linear regression and linear mixed-effects models were conducted to study cross-sectional and longitudinal interactions between KL-VS heterozygosity and APOE-ε4 on FreeSurfer-derived hippocampal volumes, neuropsychological test scores, and plasma AD biomarkers (available for a subset, n=166). Results: A significant KL-VShet+ by APOE-ε4 interaction was observed in longitudinal right hippocampal volumes, where KL-VShet+ ε4-carriers had similar rates of hippocampal atrophy compared to ε4-noncarriers, and slower rates compared to KL-VShet- ε4-carriers (β=52.94, SE=25.03, p=0.03). No significant interactions were found for any other variables. Conclusion: Our study provides evidence to suggest that KL-VS heterozygosity attenuates the detrimental effects of APOE-ε4 on brain structure in healthy elderly adults. “

POSTER N.º 11

Introduced by: Fernández Acosta, Francisco José

Title:

IMPACT OF APOE POLYMORPHISM AND G206D-PSEN1 MUTATION ON HIPPOCAMPAL NEURONS FROM ALZHEIMER´S DISEASE PATIENTS

Principal Investigator: Rebeca Vecino

Authors: R. Vecino1,2, E. Díaz-Guerra1,2, FJ. Fernández Acosta1,2, E. Arribas-González1,2, S. Alberquilla1,2, L. Vicario del Río1, M. Sánchez Calvo1, A. Orellana2,3, L. Boveda1, E. P. Moreno-Jiménez1,2, E. Soriano2,4, JM. García Verdugo2,5, A. Ruiz2,3, R. Moratalla1,2, C. Vicario1,2.

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Abstract:
Alzheimer´s disease (AD) is characterized by progressive neurodegeneration of the main brain areas involved in memory function, namely the entorhinal cortex and hippocampus. The human APOE polymorphism, more specifically the presence of the ε4 allele (coding the APOE4 protein isoform), represents a genetic form of late-onset AD, while mutations in the PSEN1 gene are responsible for many cases of early-onset familial AD. There is increasing evidence of APOE4 being involved in numerous aspects of AD pathogenesis, but the impact of APOE alleles on human neuronal maturation, function and degeneration remains to be fully elucidated. Furthermore, the effect of G206D-PSEN1 mutation on human neurons has been little explored. Using induced pluripotent stem cells (iPSCs) derived from fibroblasts of AD patients carrying the ε3 and ε4 alleles (in homozygosis) or having the G206D-PSEN1 mutation, and from healthy patients, hippocampal neurons were obtained by adding small molecules and growth factors. iPSC-derived neurons expressed hippocampal markers and showed a functional profile, illustrated by glutamate release, electrical activity and synapse formation visualized by electron microscopy and synaptic bouton analysis. In addition, the role of APOE4 in neurodegeneration was confirmed by determining amyloid-beta 42/40, total Tau and phosphorylated Tau in the culture medium, as well as by the presence of an increased number of extracellular amyloid-beta-like plaques and intracellular p-Tau181 aggregates. Finally, APOE polymorphism also affected neuronal morphology and the number of synaptic boutons. Overall, our results point to specific actions of APOE polymorphism and G206D-PSEN1 mutation affecting neuronal maturation, dysfunction and neurodegeneration in AD.

POSTER N.º 12

Introduced by: Burgueño García, Iván

Title:

HIPPOCAMPAL SCLEROSIS IN ALZHEIMER'S DISEASE: DIFFERENTIAL FEATURES IN PATIENTS WITH EARLY ONSET.

Principal Investigator: Iván Burgueño García

Authors: Burgueño-García I1,Saiz-Aúz L1, Ruiz P1, Uceda-Heras A1, López-Martínez MJ1, Rodrigo Lara H2, Rábano A1.

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Abstract:
"INTRODUCTION Hippocampal sclerosis of aging (HS) is defined by severe neuronal loss in the hippocampal cortex, especially in the subiculum-CA1 sectors. HS is primarily related to advanced age, is highly associated with limbic-predominant age-related TDP-43 encephalopathy (LATE) and combines frequently with other highly prevalent pathologies such as Alzheimer's disease (AD) or Lewy body dementia (LBD). In order to address the double association of HS to age and main neurodegenerative causes of dementia here we analyse HS and LATE in two cohorts of late (LOAD) and early onset AD (EOAD) patients, respectively. MATERIALS AND METHODS A total of 106 donated brains from the Vallecas Alzheimer's Reina Sofía (VARS) cohort were included in the LOAD group, while 56 additional brains donated to the CIEN Tissue Bank (CIEN-TB) or the Murcia Region Brain Bank form the EOAD series. The basic data set of the CIEN-TB, including full neuropathological classification of patients, was included in the analysis. For the evaluation of HS, a scale (0-4) recently proposed by our group was used, distinguishing between early (0-2) and late (3-4) HS. RESULTS Whereas LOAD brains showed a higher prevalence of HS (any stage), the proportion of advanced HS was higher in the EOAD group ($p<0.05$). Correlation (CC) between HS stage and both survival time and age at death ($p<0.001$) was highest for EOAD. Similarly, the EOAD group showed the highest CC between HS and LATE stages. CONCLUSIONS EOAD may be associated with a specific clinico-pathological profile of HS that deserves further research in larger cohorts.

POSTER N.º 13

Introduced by: Madrid Lafarga, Nerea

Title:

CHARACTERIZATION OF HIPPOCAMPAL MICROINFARCTS IN POST-MORTEM TISSUE: RESULTS FROM TWO BRAIN BANK COHORTS

Principal Investigator: Nerea Madrid

Authors: "Nerea Madrid Iván Burgueño Alicia Uceda Paloma Ruiz Laura Saiz María José López Martínez Alberto Rábano"

Filiation: Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain

Abstract:
"In aged and advanced dementia patients the combination of highly prevalent pathological conditions (e.g., Alzheimer's, Lewy body and cerebrovascular diseases, as well as limbic-predominant age-related TDP-43 encephalopathy) is most common, with specific lesions in the hippocampal formation. Accordingly, neuropathological phenotyping requires a full characterization of all pathologies involved. Cerebrovascular pathology is particularly variable and difficult to classify, and here we present our experience in the identification and description of microinfarcts in the hippocampus. The full neuropathological and clinical dataset of a large series of brains (n=414) from two brain banks (BT-CIEN and BCRM) were included in the study. Patients were either participants in the VARS dementia cohort (n=166), or external donors (n=248). A full neuropathological work-up was done in the left hemibrain, which included the examination of histological sections from the head and body of the hippocampus. Microinfarcts (MxI) were identified, counted, measured and classified morphologically, and its location within the hippocampal architecture was registered. 9.2% of brains showed hippocampal microinfarcts, and no difference was observed between the cohorts. As expected, cerebrovascular pathology scores were higher in MxI(+), that belonged predominantly to the vascular and mixed dementia diagnostic groups. Most MxI(+) cases were TDP-43(-). A morphological classification of hippocampal microinfarcts is proposed. MxI were most frequent in the CA1 and CA2 sectors of the hippocampal body. A systematic approach to the identification of MxI in the hippocampus, as the one here proposed, will help in the assessment of the contribution of cerebrovascular pathology to cognitive decline in dementia patients."

ABSTRACTS BOOK 2024

POSTER N.º 14

Introduced by: López González, Francisco Javier

Title:

A PRELIMINARY ANALYSIS ON PRECUNEUS SHAPE CHANGES IN ALZHEIMER'S DISEASE

Principal Investigator: Emiliano Bruner

Authors: Emiliano Bruner1,2, Rafael Gallareto 3, Francisco J. López-González 2, Linda Zhang2, Michel J. Grothe 2, Pascual Sánchez-Juan 2

Filiation: 1 Museo Nacional de Ciencias Naturales, CSIC, Madrid, Spain; 2 Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain; 3 Universidad de Burgos, Burgos, Spain

Abstract:
"The precuneus suffers structural, functional, and metabolic impairments during the prodromal and early stages of Alzheimer's Disease (AD). However, most of the information on the corresponding anatomical changes comes from imaging methods that do not preserve the original morphology and homology of the involved cerebral regions. In this preliminary study, we consider whether some of these changes can be recognized in terms of gross geometry and spatial arrangement. We compare a sample of non-AD aging individuals with a sample of patients diagnosed with Alzheimer's Disease. Geometric morphometrics was used to analyse shape differences between groups, through a landmark-based model including the precuneus boundaries and other neighboring references. After registration, differences between the two groups in the dorsal region, in terms of gross atrophy, are not patent. Instead, in AD patients there is a significant reduction of the ventral region, namely those parts contiguous with the retrosplenial cortex. These results are interpreted in terms of brain topology and morphological burden of these areas. Keywords: brain shape; geometric morphometrics; parietal lobe; atrophy; retrosplenial cortex."

POSTER N.º 15

Introduced by: Carmo e Pinto, Inês

Title:

A DECADE OF PART: FINDINGS FROM A TERTIARY CENTRE.

Principal Investigator: Inês Carmo e Pinto

Authors: Carmo e Pinto I, Fernandes M, Alves L.

Filiation: Neurology Department, Hospital Egas Moniz, Western Lisbon Local Health Unit, Lisbon, Portugal; NOVA Medical School, NOVA University Lisbon, Lisbon, Portugal.

Abstract:
“INTRODUCTION: In 2014, the term “”primary age-related tauopathy”” (PART) was introduced to describe a subset of patients clinically diagnosed with Alzheimer’s Disease (AD) who exhibit no or minimal amyloid plaques upon post-mortem examination. While PART and AD share considerable overlap, PART typically affects older individuals and is associated with milder cognitive decline. In the absence of clinical diagnostic criteria, a biomarker profile of A-/T+ and mesial temporal lobe atrophy may be considered non-specific biological and radiological markers for PART, potentially enabling its ante-mortem identification. METHDOLOGY: This unicentric, observational, retrospective study analysed consecutive patients presenting with predominant amnestic cognitive complaints and a CSF biomarker profile of A-/T+/N+ between 2014 and August 2024, as recorded in our SNAP database. Exclusion criteria included transitional amyloid and tau cutoff values, as well as clinical syndromes better accounted for by different diagnoses. RESULTS: We identified five cases compatible with PART. Clinical presentation ranged from subjective memory complaints to amnestic mild cognitive impairment, with a mean age at presentation of 77 years. None of the patients progressed to dementia. Radiological findings varied, showing patterns of mesial temporal lobe atrophy and generalized cortical atrophy. All patients had a CSF biomarker profile of A-/T+/N+. In none of these patients was the diagnosis of PART considered. Pathological confirmatory examination was not performed. CONCLUSION: Despite its introduction to the scientific community a decade ago, PART remains underrecognized by clinicians. However, the increasing use of ante-mortem biomarkers holds promise for improving diagnostic accuracy, drawing attention to this neurodegenerative disorder.”

POSTER N.º 16

Introduced by: Valeriano Lorenzo, Elizabeth Lucía

Title:

LEVELS OF P-TAU217 IN BLOOD AND ITS CAPACITY TO PREDICT CHANGE PATTERNS OF COGNITIVE TRAJECTORIES IN ELDERLY

Principal Investigator: Elizabeth Valeriano Lorenzo

Authors: Elizabeth Valeriano-Lorenzo1,2, David García3, Sonia Wagner 1, Alicia Ruiz 1, Ana Belén Pastor 1, Belén Frades 1, Meritxell Valentí 1, Mario Riccardi 1, Ma Ascencion Zea1, Marta Antón1, Teodoro del Ser1, Pascual Sánchez-Juan1.

Filiation: 1Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2Universidad Autónoma de Madrid, Madrid, Spain. 3Universidad Complutense de Madrid, Madrid, Spain.

Abstract:
“Aim Longitudinal trajectories of cognitive performance in older adults are non-homogeneous across time. For this reason, one approach to capturing that heterogeneity is the estimation of patterns of change or latent classes (LC) that explain the formation of groups of subjects with stable or changing cognitive trajectories. We conducted this study to analyse the effect of baseline plasma p-tau217 levels on cognitive change patterns in the elderly. Methods 913 participants, cognitively healthy at baseline, from the Vallecas Project, were selected (583 women, 64%) with a mean baseline age of 73.8±3.8 years and an average follow-up of 10.2±0.6 years. Patterns of change based on the non-linear trajectories of 5 cognitive domains were analysed using Growth Mixed Models (GMM) and adjusting for educational level, baseline age, sex and number of drugs in the medication list. Three LCs explaining individual cognitive change were obtained, and then the distribution of baseline plasma p-tau217 levels and other relevant clinical variables were examined according to the previously established LCs. Results The group with a stable pattern of their cognitive trajectory shows significantly lower concentrations of p-tau217 than the groups with slight cognitive decline or markedly declining, in domains such as delayed verbal memory (P<.001), semantic fluency (P<.001), and processing speed (p < 0.001). In addition, a lower number of drugs in the medication list consumed, a greater speed and motor control ability, lower depression indicators and other clinical variables characterise the group with stable patterns in their cognition. Conclusions Significantly lower concentrations of plasma p-tau217 are associated with a stable longitudinal change pattern and therefore a lower probability of accumulation of AD pathology. Keywords: blood biomarkers, p-tau217, cognitive change pattern, growth mixture model.”

POSTER N.º 17

Introduced by: Marta Aramburu-Núñez

Title:

NOVEL P-TAU MONOCLONAL ANTIBODY-BASED IN-VITRO AND PRECLINICAL THERAGNOSTIC STUDIES FOR TAUOPATHIES

Principal Investigator: Marta Aramburu Núñez

Authors: Marta Aramburu-Núñez1,2, Lara García-Varela2,3,4, Antía Custodia1,2, Noemí Gómez-Lado2,3,4, Mónica Castro-Mosquera1, Mariña Rodríguez-Arrizabalaga1, Manuel Debasa-Mouce1, Juan Manuel Pías-Peleteiro1,2, José Manuel Aldrey1,2, Daniel Romaus-Sanjurjo1,2, Alberto Ouro1,2, Pablo Aguiar2,3,4, Tomás Sobrino1,2.

Filiation: 1NeuroAging Laboratory Group, Clinical Neurosciences Research Laboratory, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain. 2Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain. 3Molecular Imaging Group, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain. 4Molecular Imaging Biomarkers and Pharmacokinetic Modelling, Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), University of Santiago de Compostela, Spain.

Abstract:
Tauopathies are the primary cause of older people losing their sense of autonomy, which suggests a steady reduction in cognitive function. Early diagnosis of tauopathies is not associated with a successful therapy. Using a new phosphorylated Tau (p-Tau) monoclonal antibody (mAb), which is responsible for tau self-aggregation and control, we present an in-vitro and theragnostic method. In order to identify p-Tau in 89 cerebrospinal fluid (CSF) samples from individuals with moderate cognitive impairment(MCI) and Alzheimer's disease(AD), a diagnostic Sandwich ELISA kit was created. The levels of the tau isoforms exhibited the same behaviour with a rise in CSF as the disease develops, and the proof-of-concept study produced distinct signals beyond the limit of detection while retaining a low intra-assay coefficient of variation. Additionally, we evaluated the impact of p-Tau mAb on behaviour and brain functions in transgenic mice models of tauopathy delivered intraventricularly. According to the findings, p-Tau mAb therapy for four weeks decreased p-Tau levels in the cortex and hippocampus and enhanced motor outcome by postponing hindlimb clasping and latency to fall in the rotarod test. Moreover,p-Tau mAb was radiolabelled with 89Zr and the results in transgenic mice showed that the mAb-89Zr were stable in circulation up to 10 days, but the amount reaching the brain was <0.2%. These findings demonstrated a new theragnostic p-Tau mAb that identifies an early p-Tau biomarker in AD patients.Therefore, it is essential to enhance the quantity of mAb that enters the brain and multicenter clinical studies are required to verify these encouraging results.

POSTER N.º 18

Introduced by: Moreno Gonzalez, Ines

Title:

LATE-LIFE DEPRESSION EXACERBATES COGNITIVE IMPAIRMENT AND TAU-ASSOCIATED PATHOLOGY IN P301S MICE

Principal Investigator: Ines Moreno-Gonzalez

Authors: Vegas-Gomez L1, Arredondo-Alcala MA1, Gutierrez A1,2, Moreno-Gonzalez I1.

Filiation: 1 Departamento Biologia Celular, Genetica y Fisiologia, Instituto de Investigacion Biomedica de Malaga-IBIMA, Facultad de Ciencias, Universidad de Malaga. 2 Centro de Investigacion Biomedica en Red Sobre Enfermedades Neurodegenerativas (CIBERNED)

Abstract:
Recent studies suggest that depression may be a crucial risk factor for the development of cognitive impairment and Alzheimer's disease (AD). There is a strong association between late-life depression and AD, with the onset of AD being accelerated in patients with mild cognitive impairment (MCI) who have a history of depression. Women appear to be particularly vulnerable to this condition. In addition, individuals with MCI who present depressive symptoms have an elevated burden of amyloid-beta (Aβ), the main toxic protein associated with Alzheimer's pathology, and an increased risk of developing AD compared to non-depressed MCI patients. While some transgenic models of AD exhibit depression-like symptoms in advanced stages, the induction of Alzheimer's pathology due to a depressive process has not been thoroughly studied under experimental conditions that emulate late-life depression as a risk factor for AD. The objective of this study is to determine whether depression is a cause, rather than a consequence, of AD development by inducing unpredictable mild chronic stress (CUMS) in tau transgenic P301S mice. Our results indicate that CUMS induction in transgenic animals leads to phenotypic changes related to a depressive state. Behavioral and histological studies suggest that depression-like induction can worse AD pathology. The findings from this project could provide evidence of depression as a risk factor for AD, elucidate its mechanisms of action, identify new early biomarkers, and contribute to the discovery of new therapies for AD.

POSTER N.º 19

Introduced by: López Martínez, María José

Title:

COPATHOLOGY IN PROGRESSIVE SUPRANUCLEAR PALSY: A SPECTRUM OF PATTERNS AND POTENTIAL SYNERGIES

Principal Investigator: María José López Martínez

Authors: María José López Martínez (1), Héctor Rodrigo Lara (2), Laura Sáiz Auz (1), Paloma Ruiz Valderrey (1), Iván Burgueño García (1), Alicia Uceda Heras (1), Alberto Rábano Gutiérrez (1)

Filiation: "1. Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2. Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain."

Abstract:
"Introduction: Progressive supranuclear palsy (PSP) is a sporadic 4-repeat tauopathy with cortical and subcortical involvement. The regional distribution of neuronal loss and tau pathology, and the coexistence of PSP with other neurodegenerative diseases are sources of phenotypical variability. Objectives: Our aim is to analyze the frequency and severity of copathologies in patients with neuropathological diagnosis of PSP. Materials and Methods We analyze a case-series including all PSP cases with neuropathological evaluation in the Neurological Tissue Bank of the CIEN Foundation in Madrid, Spain. We assessed copathologies according to standardized diagnostic criteria and current staging schemes. Results: From 37 patients included, 65% were male. Mean age at death was 75 years (IQR 70-83). Antemortem clinical diagnosis of PSP was made in 54% of cases. Isolated PSP pathology was observed in 24% of brains. The remaining cases exhibited a broad spectrum of combined pathologies: argyrophilic grain disease in 46% of patients, Alzheimer's disease neuropathologic change in 38% of patients and Lewy body pathology in 8% of cases. Corticobasal degeneration overlapped with PSP in 3 cases. One case showed limbic-predominant age-related TDP-43 encephalopathy (LATE) with hippocampal sclerosis, and 2 cases had hippocampal sclerosis with Pick-like hippocampal spherical inclusions in the absence of TDP-43 immunoreactivity. One patient had a genetically confirmed diagnosis of Huntington's disease, which was found to be combined with PSP in the neuropathologic workup. Conclusions: Mixed pathologies are widely prevalent in PSP, brain autopsies remain useful for a better understanding of potential disease synergies and its further impact on targeted therapies.

POSTER N.º 20

Introduced by: Sevilla, Mª Ascension

Title:

FRONTOTEMPORAL DEMENTIA (FTD) - MADRID CONSORTIUM. CREATION OF AN FTD STUDY COHORT FOR THE VALIDATION OF CUTTING EDGE BIOMARKERS

Principal Investigator: Mª Ascension Zea Sevilla

Authors: Mª Ascensión Zea Sevilla1, Frontotemporal Dementia Madrid Consortium2,María Belen Frades Payo1,Elizabeth Valeriano-Lorenzo1, Francisco J López1 Mª,Meritxell Valenti1, Mario Ricciardi,. Isabel López1 Alicia Ruiz1, Sonia Wagner1. Ana Belén Pastor1, Minerva Martinez1, Teodoro del Ser1 Alberto Rábano 1, MªJose López Martínez 1, Alicia Uceda 1, Paloma Ruiz1, Laura Saiz 1, Nekane Moreno . 1, Marta Antón Michel Grothe1 Pascual Sánchez-Juan1

Filiation: 1. Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2. Memory Clinics of the Autonomous Community of Madrid (CAM)

Abstract:
“Background FTD is the third cause of neurodegenerative dementia in our environment. The diagnosis is complex and usually uncertain without neuropathological study. Therefore, the development of any diagnostic technique or biomarker would be of paramount importance for clinical practice. The most common “misfolded” proteins in FTD are Tau and TDP-43. Identifying specific pathogenic species of tau and TDP-43 correlated with the disease would represent a straightforward diagnosis approach. Material and methods The FTD-Madrid Consortium is a multicenter project, coordinated by CIEN, to recruit a cohort of FTD patients with behavioral variant or primary progressive aphasia. A clinical assessment, plasma biomarkers, cerebrospinal fluid analyses, and neuroimaging will be performed on every participant. All the Memory Clinics of the Autonomous Community of Madrid (CAM) participate in this project. The RT-QuIC (Real-Time Quaking-Induced Conversion), a seeding assay technique, will be evaluated to detect pathogenic isoforms of 3R and 4R tau, and with SIMOA technology we will quantify TDP-43 in extracellular vesicles. Also, we will test the diagnostic utility of a set of plasma/CSF biomarkers determined by the SIMOA technique (TDP43, p-Tau 181, t-Tau, ABeta 40, ABeta42, NfL and GFAP) and its combination with RT-QuIC. In a neuropathological cohort from the CIEN Biobank we will also study the same biomarkers trying to validate them. The project is funded by Carlos III Health Institute (PI23/01314. AES-ISCIII). Current Situation Patient recruitment has just started. Conclusions We are committed to creating a deeply phenotyped cohort of FTD patients, aiming to validate new biomarkers, improve the diagnosis of FTD by integrating precision medicine tools, and create a patient identification platform for future clinical trials.

POSTER N.º 21

Introduced by: Mirfakhar, Farzane

Title:

CHARACTERIZATION OF LYSOSOMAL DYSFUNCTION IN STEM CELL MODELS OF FRONTOTEMPORAL DEMENTIA USING SUPER RESOLUTION MICROSCOPY

Principal Investigator: Farzaneh S. Mirfakhar

Authors: Farzaneh S. Mirfakhar[1], Jacob A. Marsh[1], Miguel Minaya[1], David Perlmutter[2], Celeste M. Karch[13]

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Abstract:

“Objectives Impaired proteostasis has been implicated in frontotemporal dementia with tau inclusions (FTD-tau). This impairment may lead to the accumulation of the tau protein. Here, we sought to determine whether MAPT mutations that cause FTD-tau impact tau degradation by the lysosome. Methods Human induced pluripotent stem cells (iPSC) expressing MAPT p.R406W and isogenic controls with NGN2 stably expressed within the AAV safe harbor locus. Neurons were cultured for 14 days and evaluated by super resolution microscopy. Results MAPT p.R406W neurons displayed morphological and functional deficits in the lysosomes, including elevated size and density of LAMP1-positive vesicles. These phenotypes were reversed upon correction of the mutant allele with CRISPR/Cas9. Given these lysosomal defects, we sought to investigate the impact on lysosomal-mediated tau degradation using super resolution microscopy. MAPT p.R406W neurons exhibited fewer empty lysosomes compared to isogenic controls, suggesting the degradative capacity is reduced in these vesicles. MAPT p.R406W neurons exhibited a significant increase in tau-retention in the membrane and lumen of LAMP1-positive vesicles compared to isogenic controls. Interestingly, tau phosphorylated at pThr231 was significantly enriched in the membrane of LAMP1-positive vesicles compared to isogenic controls, suggesting defects in the transport of pTau-231 into the lysosome. Time-lapse live imaging data revealed that lysosomes in MAPT p.R406W neurons travel shorter distances and at slower speed while FRAP analysis illustrated similar microtubule stability in MAPT p.R406W and isogenic control neurons. Conclusions Together, our findings suggest that MAPT p.R406W may be sufficient to cause impaired lysosomal function leading to disrupted tau degradation by lysosomes, which may contribute to the development of tau pathology.

POSTER N.º 22

Introduced by: Naranjo, José Ramón

Title:

DREAM LIGANDS ACTIVATE UPR-DEPENDENT NEUROPROTECTION IN A TDP-43 MOUSE MODEL OF FRONTOTEMPORAL LOBAR DEGENERATION

Principal Investigator: Gonzalo-Gobernado, Rafael

Authors: Rafael Gonzalo Gobernado1,2, Paz González 1, Xose M. Dopazo 1,2, Damián Tandalla2, Britt Mellström1,2 and José R. Naranjo1,2.

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Abstract:
“DREAM ligands activate UPR-dependent neuroprotection in a TDP-43 mouse model of Frontotemporal Lobar Degeneration Rafael Gonzalo Gobernado1,2, Paz González 1, Xose M. Dopazo 1,2, Damián Tandalla2, Britt Mellström1,2 and José R. Naranjo1,2. 1 Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain. (rd.gonzalo@cnb.csic.es, naranjo@cnb.csic.es) 2 Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain. (rd.gonzalo@cnb.csic.es, naranjo@cnb.csic.es) Funding: CIBERNED (PI2022/02), Asahi Kasei Pharma and Fundación Luzón Frontotemporal dementia is a neurodegenerative syndrome that encompasses a heterogeneous group of diseases, all of which have in common the degeneration of the frontal and temporal lobes (Frontotemporal Lobar Degeneration, FTLD). Patients exhibit personality changes, social behaviour and language problems, amnesia and movement disorders. Around 45% of FTLD patients present neuronal cytoplasmic inclusions of TDP-43, a phenomenon considered as a key pathological feature. The aggregation of TDP-43 and ubiquitinated proteins alters proteostasis and triggers the unfolded protein response (UPR). Our group identified the interaction of ATF6, a UPR key regulator, with the neuronal calcium sensor DREAM, as a potential therapeutic target in neurodegeneration, and demonstrated that the modulation of this interaction using DREAM binding molecules exerted neuroprotection in models of neurodegenerative diseases. The aim of this work was to study the potential neuroprotective effect of repaglinide, a known DREAM binding molecule, in the hTDP-43/CamKII□ mouse model of FTLD Repaglinide treatment increased lifespan, improved social deficits (3-chamber test) and cognitive impairment (Novel Object Recognition, marble burying and Y-maze tests) of TDP-43 mice. Furthermore, TDP-43 animals treated with repaglinide showed reduced neuronal loss and microgliosis and an increased ATF6 processing in the frontal cortex. These findings suggest that the modulation of the DREAM-ATF6 interaction by repaglinide improves FLTD-related symptoms and neuronal loss, potentially through the regulation of ATF6 signaling. Further research will be needed to fully elucidate the mechanisms of action by which repaglinide ameliorates FTLD progression in this model of TDP-43-mediated pathology.

POSTER N.º 23

Introduced by: Martínez Castillo, Minerva

Title:

PLASMA EXTRACELLULAR VESICLES AS A POTENTIAL BIOMARKER IN AMYOTROPHIC LATERAL SCLEROSIS

Principal Investigator: Minerva Martinez-Castillo

Authors: Minerva Martinez-Castillo1, Sonia Wagner-Reguero1, Alicia González Ruiz 1, Iván Burgueño-García 1, Paloma Ruiz-Valderrey 1, Laura Saiz-Aúz 1, Pamela Martino-Adami 2, Selçuk Özdemir3, Alberto García-Redondo4, Alberto Rábano 1, Alfredo Ramirez 2,3,5,6,7, Anja Schneider 3, Pascual Sánchez-Juan 1

Filiation: 1Alzheimer's Centre Reina Sofia-CIEN Foundation-ISCIII. Madrid, Spain. 2Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne. Cologne, Germany. 3German Center for Neurodegenerative Diseases (DZNE). Bonn, Germany. 4ALS Research Laboratory Unit, Department of Neurology, Hospital Universitario 12 de Octubre. Madrid, Spain. 5Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Medical Faculty. Bonn, Germany. 6Department of Psychiatry and Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases. San Antonio, United States of America. 7Cluster of Excellence Cellular Stress Responses in Aging associated Diseases (CECAD), University of Cologne. Cologne, Germany.

Abstract:
Protein TDP-43 accumulates in more than 95% of the brains of ALS patients, which normally occurs within the nucleus of brain cells but is localised in atypical regions in these patients. Detection of TDP-43 in the cerebrospinal fluid or blood of ALS patients is a potential diagnostic biomarker of great interest. However, determinations of this free protein have not been successful in diagnosing neurodegenerative diseases. The CIEN Foundation, in collaboration with the research groups of Prof. Dr. Anja Schneider (DZNE, Bonn, Germany) and Prof. Dr. Alfredo Ramirez (Uniklinik Köln, Germany), has just started a new project to study TDP-43 not in free form but within extracellular vesicles (EVs) circulating in the blood. Isolation and characterisation of EVs are performed in plasma samples, following serial centrifugation steps and size exclusion chromatography to purify small (≈80-150 nm) and medium (≈100-400 nm) EVs. Concentration of TDP-43 and other potential biomarkers in the vesicular interior are measured using the ultrasensitive Simoa. The determination of vesicle number and size is carried out by Nanoparticle Tracking Analysis (NTA). In addition, it is intended to further characterise neuropathological samples from ALS patients by quantification of histological lesions. In this way, neuropathological findings could be correlated with these biomarkers, and proteomic analyses both in their free and intravesicular form could be carried out. In conclusion, the aim is to discover peripheral biomarkers that will allow us to make an early and accurate diagnosis of ALS, as well as to estimate disease progression and eventual responses to future treatments.

POSTER N.º 24

Introduced by: Conte, Carmela

Title:

TOLL-LIKE RECEPTOR 4 UPREGULATION IN THE SUBSTANTIA NIGRA PARS COMPACTA AND MEDIAL TEMPORAL GYRUS FROM PARKINSON'S DISEASE PATIENTS: A POTENTIAL MECHANISM DRIVING INFLAMMATORY RESPONSE.

Principal Investigator: Carmela Conte

Authors: Carmela Conte1*, Angela Ingrassia2, John Brevè2, John J. Bol2, Evelien Timmermans-Huisman2, Anne-Marie van Dam2, Tommaso Beccari1 and Wilma D. J. van de Berg2.

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Abstract:
"Introduction Neuroinflammation and immune dysfunction play a critical role in the pathophysiology of Parkinson's disease (PD) and correlates with the accumulation and aggregation of alpha-synuclein (αSyn). Toll-like receptors (TLRs) are a group of innate immune receptors widely distributed in the CNS able to sense several exogenous and endogenous stimuli which trigger inflammatory responses and cause the accumulation of αSyn. On the other hand, αSyn can bind the TLRs and evoke an inflammatory response in attempt to clear itself and restore brain homeostasis. Therefore, the precise role of TLRs is debated as helpful and harmful effects can occur. In the present study, we investigated the expression levels of TLR4 and αSyn in substantia nigra (SN) and medial temporal gyrus (GTM) of patients with PD. Moreover, we analysed the posphpS129 αSyn (pS129 αSyn) levels considered the most common used marker of αSyn pathology, and the possible co-localization with TLR4. Moreover, we examined Iba1 expression as a marker of microglia activation, and its co-localization with TLR4. Materials and methods Post-mortem human brain tissue was obtained from the Netherlands Brain Bank and the Department of Anatomy and Neurosciences of VU University Medical Center (VUmc, Amsterdam, The Netherlands). A total of 60 samples (15 cases and 15 control donors per GTM and SN) were analysed by qPCR. A total of 25 samples (6 PD/PDD donors and 6 controls for GTM; 6 PD/PDD donors and 7 controlled cases for SN) were analysed by immunofluorescence and confocal microscopy for TLR4, pS129-αSyn, and Iba1. The presence of somatic pS129-αSyn immunoreactivity was used to distinguish between cells with and without cytopathology. Results In the present study, we observed that the levels of TLR4 were increased in the SN and GTM of patients with PD, while αSyn was downregulated, probably because of the significant depletion of dopaminergic neurons. In PD patients, we also found co-localization between TLR4 and pS129-αSyn and between TLR4 and glial Iba-1 in SN Lewy bodies and pyramidal neurons within GTM compared with the same regions of the control donors. Conclusions Our findings provide evidence that TLR4 is up-regulated in PD patients. Moreover, the co-localizations between TLR4 and pSer129-αSyn and Iba1 suggest a physical interaction that may evoke the activation of inflammatory response.

POSTER N.º 25

Introduced by: Rivas Santisteban, Rafael

Title:

CANNABINOIDS AND ANGIOTENSIN II MODULATE CALCIUM HANDLING IN STRIATAL NEURONS

Principal Investigator: Rafael Rivas-Santisteban

Authors: Rafael Rivas-Santisteban1,2, Ana Muñoz2,3, Jaume Lillo2,4, Iu Raïch2,4, Ana I. Rodríguez-Pérez2,3, Gemma Navarro2,4*, José L. Labandeira-García2,3*, Rafael Franco2,6,7

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Abstract:

"Parkinson's disease (PD) is a neurodegenerative condition characterized by the degeneration of dopaminergic neurons within the substantia nigra, which results in motor dysfunction. Current therapeutic approaches primarily aim to manage symptoms, highlighting the urgent need for interventions that address the root cause of neuronal death. Emerging evidence in the scientific literature suggests that the endocannabinoid system, particularly through the activation of cannabinoid receptor 1 (CB1R)—the most prevalent G protein-coupled receptor (GPCR) in central nervous system (CNS) neurons—holds promise for neuroprotection in PD. This study examines the interaction between the CB1R and the angiotensin II type 1 receptor (AT1R), the latter being involved in maintaining neuronal calcium homeostasis, a crucial factor in neurodegeneration and cell death. We explored the functional dynamics of the AT1-CB1 receptor complex (AT1CB1Hets) concerning signaling pathways and its potential role in PD pathophysiology. Notably, our findings revealed that CB1R-selective agonist (ACEA) and antagonist (rimonabant) modulated calcium signaling induced by AT1R activation. The direct association between these receptors to form AT1-CB1 heteromers (AT1CB1Hets) was confirmed through bioluminescence resonance energy transfer (BRET2) assays. Additionally, our results indicate that cannabinoids decrease AT1R-mediated signaling in striatal neurons. In situ proximity ligation assays (PLA) further validated the formation of AT1CB1Hets in neurons, with a higher prevalence of these complexes near the neuronal soma (NeuN positive) as compared to more distant regions such as dendrites (MAP2 positive). Furthermore, AT1CB1Hets expression was evaluated in the striatal neurons of rats subjected to a 6-hydroxydopamine (6-OHDA) model of PD. A reduction in AT1CB1Hets expression was observed in neurons from lesioned animals relative to non-lesioned controls. Interestingly, AT1CB1Het expression fluctuated depending on the lesion status and the effects of L-DOPA treatment, such as the development of dyskinesias versus the absence of involuntary movements. In animals that exhibited L-DOPA-induced dyskinesias, a partial restoration of AT1CB1Het expression was noted. These findings suggest that AT1CB1Hets may play a compensatory role in modulating the susceptibility to L-DOPA-induced dyskinesias in Parkinson's disease.

ABSTRACTS BOOK 2024

POSTER N.º 26

Introduced by: Monteiro, Sara

Title:

CEREBRAL BLOOD FLOW DYNAMICS IN A PARKINSONIAN MOUSE LINE

Principal Investigator: Sara Pires Monteiro

Authors: “Sara Pires Monteiro Ruxanda Lungu Patricia Figueiredo Noam Shemesh”

Abstract:
Parkinson’s disease (PD) is a prevalent neurodegenerative disorder typically manifesting α-synuclein (α-syn) deposition, loss of dopaminergic neurons, brain atrophy, severe motor symptoms and cognitive decline. Interestingly, the vascular system may be also implicated in the disease, with patients also reported to exhibit reduced venous outflow and lower perfusion compared to healthy subjects. Here, we harness a mouse model of PD exhibiting extensive human α-syn deposition to investigate cerebral blood flow properties in PD. We use a novel setup enabling high resolution Pseudo-Continuous Arterial Spin Labelling, a non-invasive technique for perfusion mapping in-vivo without injection of contrast agents. Adult C57BL/g mice (~20 weeks old, weights 25–30g) (N=3), the transgenic αSYN mouse model (C57BL/6-DBA/2 Thy1- αSYN) (N=3) and their wildtype littermates (healthy controls, N=3) 36-42 weeks of age and weighing 42±15g, were housed in 12h/12h light/dark cycles with ad-libitum access to food and water. Animals were sedated using 1.5-2.5% isoflurane. Respiratory rate was kept at 60-90bpm. An unbalanced pCASL sequence was used as described in Hirschler et al. (2018). The mice were positioned on top of a custom-built ramp to control carotid positioning for increased labelling efficiency. The labelling plane was positioned at the mouse neck (~8mm below the isocenter), labelling duration (LD)=3s, post-labelling delay (PLD)=300ms. A single-shot EPI was implemented: FOV=12x12mm2, slice thickness=0.5mm, spatial resolution=100x100m2, TR/TE=4000/25ms, 30 repetitions, Tacq=4min. For cerebral blood flow (CBF) quantification, the T1 map was obtained from an inversion recovery sequence. A pCASL encoded FLASH was employed to estimate the inversion efficiency (IE) 3mm above the labelling plane (PLD=0ms, LD=200ms). CBF maps (ml/100g/min) was calculated pixel-by-pixel to obtain high resolution CBF maps. T-tests were used to compare the average whole-brain CBF values across 3 different groups. In the CBF maps, clear differences in perfusion brain-wide can be observed with pronounced increased perfusion in the PD and their WT littermates when compared to the C57BL/g are obvious, mostly in cortical and thalamic regions. Distributions across animals of the whole-brain average CBF further show that the PD model shows significantly increased perfusion compared to the C57BL/g mouse line, but not compared to its wildtype littermates, which also exhibit higher CBF than the C57BL/g (paired t tests, $p<0.05$). Our findings suggest that the PD mouse line and their WT littermates have altered perfusion properties across their entire brains compared to control C57bl/6 mice. Thus, local effects of α-syn deposition may not fully explain the altered vascular properties. The much higher values compared with the standard C57BL/g mouse line likely reflect either an underlying genetic difference between the strains causing higher perfusion in the PD line, or otherwise reflect other auxiliary factors (e.g. how isoflurane affects perfusion between the lines). Future experiments in awake animals and physiological measurements of e.g. heart-rate, blood pressure, and vascular density could further narrow down the sources of these differences. Nevertheless, our findings highlight the importance of accounting for these potential sources of variability in future work with these lines

POSTER N.º 27

Introduced by: Ruiz, Alicia

Title:

POST-MORTEM CSF FOR DETECTING A- SYNUCLEIN SEEDING.

Principal Investigator: González Ruiz. A

Authors: González Ruiz. A1, Wagner Reguero. S 1, Pastor. AB1, Ruiz Calvo. A1, Martínez. M1, Moreno Manzano. N1, Burgueño García. I 1, Saiz Aúz 1 . L, Rábano Gutiérrez. A1, Schmitz. M2, Canaslan. S 2, Zerr. I 2, Sánchez Juan. P1 .

Filiation: 1. Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2.Department of Neurology, National Reference Center for TSE, The German Center for Neurodegenerative Diseases (DZNE), Georg-August-University, University Medicine Göttingen, Göttingen, Germany.

Abstract:

"Synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are characterized by the accumulation of misfolded α-synuclein aggregates in the central nervous system. Seed amplification assay (SAA), such as real time quaking-induced conversion (RT-QUIC), have emerged as highly sensitive and specific method for detecting this misfolded α – synuclein in biological samples. The main fluid used is cerebrospinal fluid (CSF). There are a few publications demonstrating the usefulness of postmortem CSF for RT-QUIC. Our aim is to validate post-mortem CSF S to detect the α-synuclein seeding by RT-QUIC. Ten postmortem CSF samples were collected from VARS project participants, classified according to their neuropathological diagnoses. •

Synucleinopathy group: Four participants neuropathologically diagnosed as DLB and one as PD. •

ALS group: Five participants neuropathologically diagnosed as amyotrophic lateral sclerosis (ALS). This assay was performed at the Universitätsmedizin laboratory in Göttingen, Germany. Each sample was run in triplicate by the FluoStar Omega Series over 24 hours. In the synucleinopathy group, three participants diagnosed as DLB were considered positives, their triplicates got amplification (3/3) and crossed Threshold (Fmean1: 11,051 RFU; Fmean2= 8,472 RFU and Fmean3: 16,629 RFU). On the other hand, within the ALS group, the five participants didn't get amplification and were considered as negative. These results support the utility of postmortem CSF as samples for α-synuclein SAA. The future goal will be to study a larger sample, and correlate α-synuclein seeding with neuropathological variables to validate its clinical use.

POSTER N.º 28

Introduced by: Martínez Castillo, Minerva

Title:

ASSOCIATION BETWEEN PLASMA DOPA DECARBOXYLASE AND NEUROPATHOLOGY IN DEMENTIAS: INSIGHTS FROM THE VARS COHORT

Principal Investigator: Minerva Martinez-Castillo

Authors: Minerva Martinez-Castillo1, Sonia Wagner-Reguero1, Iván Burgueño-García 1, Paloma Ruiz-Valderrey 1, Mario Ricciardi 1, Laura Saiz-Aúz 1, Pamela Martino-Adami 2, Alfredo Ramirez 2,3,4,5,6, Alberto Rábano 1, Pascual Sánchez-Juan 1

Filiation: 1Alzheimer's Centre Reina Sofia-CIEN Foundation-ISCIII, Madrid, Spain. 2Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne. Cologne, Germany. 3Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Medical Faculty. Bonn, Germany. 4German Center for Neurodegenerative Diseases (DZNE). Bonn, Germany. 5Department of Psychiatry and Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases. San Antonio, United States of America. 6Cluster of Excellence Cellular Stress Responses in Aging associated Diseases (CECAD), University of Cologne. Cologne, Germany.

Abstract:
DOPA decarboxylase (DDC) has been proposed as a novel cerebrospinal fluid (CSF) biomarker with increased concentrations in Lewy body disorders. However, findings on DDC levels in plasma are inconsistent between studies. Patients from Vallecas Alzheimer Reina Sofía (VARS) cohort were all demented, diagnoses were confirmed by autopsy (Alzheimer's disease [AD], N=103; vascular dementia [VD], N=14; dementia with Lewy bodies [DLB], N=12), and were classified into groups considering the depigmentation of substantia nigra (SN; 0=normal, 1=neuronal loss and gliosis, 2=massive neuronal loss and severe gliosis) followed by the quantification of neurons in this region. Plasma ante-mortem DDC levels were quantified as part of the Olink Explore 3072. DDC levels and number of neurons were compared between groups using generalized linear models, adjusted for age and sex. Correlations between plasma DDC and neuropathology were performed by Spearman's rank correlation. Plasma DDC levels were not significantly different between diagnostic groups. However, DLB subjects had lower number of neurons in SN, being this difference significant compared to AD and VD. In addition, plasma DDC levels were not significantly different between different stages of SN depigmentation. Negative association was observed between the number of neurons in SN and the main neuropathological variables for DLB (Braak stage for a-synuclein and Lewy Pathology Consensus Criteria [LPC]) but no correlation of these with plasma DDC. In contrast to CSF, plasma DDC may have limited use as a diagnostic biomarker. Even so, it is needed to consider and further study the effect of medication uses when analyzing plasma DDC.

POSTER N.º 29

Introduced by: Lungu, Ruxanda

Title:

MULTIMODAL EVALUATION OF SENSORY DEFICITS IN PARKINSON'S DISEASE: INSIGHTS FROM FMRI, C-FOS, AND CBF STUDIES

Principal Investigator: Ruxanda Lungu

Authors: "Ruxanda Lungu Francisca F. Fernandes Sara Monteiro Tiago F. Outeiro Noam Shemesh"

Abstract:
Parkinson's disease (PD) is primarily known for its severe motor symptoms and cognitive decline, but the involvement of the brain's sensory systems, including olfactory and visual deficits, is less well understood and often overlooked. In this study, we report abnormalities in BOLD-fMRI responses along the olfactory and visual pathways in an α-synuclein mouse model of PD. We validate these findings by assessing neuronal origins through C-FOS protein expression levels and ASL measurements. Our fMRI results demonstrated decreased activity in most sensory areas, which was corroborated by reduced C-FOS staining, confirming a neural basis for the observed abnormalities. Additionally, ASL measurements ruled out any vascular differences that could confound the fMRI signals, solidifying the sensory deficits as a result of PD pathology.

POSTER N.º 30

Introduced by: Saiz Aúz, Laura

Title:

GENOMICS AND DIGITAL NEUROPATHOLOGICAL PHENOTYPING OF IBERIAN BRAINS (GADIR): A CHALLENGE FOR SPANISH AND PORTUGUESE BRAIN BANKS

Principal Investigator: Laura Saiz Aúz

Authors: Laura Saiz1, Victoria Fernández2, María José López1, Alberto Rábano1, on behalf of the Neurological Tissue Banks Working Group (ISCIII Platform for Biomodels and Biobanks).

Filiation: 1 Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2 Fundacio ACE. Institut Català de Neurociènces Aplicades.

Abstract:
“GADIR is an ambitious endeavour aimed at the genomic characterization of thousands of donated brains in Spain and Portugal with a full and updated neuropathological assessment. Additionally, the project will focus on a subset of early (EOAD) and late onset (LOAD) Alzheimer’s disease brains, with deep neuropathological phenotyping and digital characterization of key histological lesions. GADIR is a 3-year project starting in autumn 2024 and based on the collaboration between CIEN and ACE Foundations. Here we present the main organizational and logistic aspects of GADIR. Over 3500 brains from 16 brain banks (BB) in Spain and Portugal with diverse neuropathological diagnoses will be studied. We estimate that around 50% of them will bear a main diagnosis of Alzheimer’s disease. Aim 1 establishes the coordination with BB for collection and harmonization of samples and associated metadata (1.1), and for revision and updating of neuropathological classification of brains (1.2). Aim 2 will be centred on genotyping of samples at CEGEN (2.1.), and calculation of polygenic risk scores for various pathologies (2.2). Aim 3 will focus on GWAs of neuropathological traits (3.1), in-silico functional exploration (3.2), and replication of findings in other datasets (3.3). Aim 4 will be directed to digitalization and AI/ML analysis of selected histological sections of 350 EOAD and LOAD brains (4.1 and 4.2), and to genome/morphology analysis for selected pathological traits (4.3). Logistics of samples and associated data and fine tuning between the coordination centres and BB will be crucial for the success of this ambitious and unique project.

POSTER N.º 31

Introduced by: Bonilla Escribano, Pablo

Title:

PREDICTING MILD COGNITIVE IMPAIRMENT IN HEALTHY INDIVIDUALS UP TO 9 YEARS BEFORE ITS ONSET: A MULTISOURCE APPROACH

Principal Investigator: Pablo Bonilla Escribano

Authors: Pablo Bonilla-Escribano1, Linda Zhang1, Teodoro Del Ser 1, Pascual Sánchez-Juan1, Jussi Tohka 2 and Bryan Strange 1,3

Filiation: "1. Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain. 2University of Eastern Finland, A.I. Virtanen Institute for Molecular Sciences, Kuopio, Finland. 3Laboratory for Clinical Neuroscience, CTB, Universidad Politécnica de Madrid, Spain"

Abstract:
"Age-associated cognitive decline is an open research question, due to the lack of accurate markers to determine which cognitively healthy individuals will undergo a neurodegenerative process at the earliest pre-clinical stages. Here, we study how different feature sources (or modalities) can predict which individuals will develop mild cognitive impairment (MCI). Data of 934 participants from the Vallecas project, cognitively normal at baseline, were used: 113 developed MCI during the 9 follow-up visits (converters), and 821 were taken as controls. Thus, this analysis simultaneously predicts MCI conversion in the next year, in two years, …, up to 9 years. An initial set of 742 features from 9 modalities, all measured at the first visit, was considered. A logistic regression regularized with an elastic net was used to parsimoniously select groups of features. The analysis was repeated for each feature source combination independently. Repeated nested cross-validation was used for model assessment and hyperparameter tuning via Bayesian optimization, thereby addressing the risk of data leakage and overfitting. The dataset was split 7 times into 25 folds across the two levels. The best performing models achieve an AUC of ~0.75. Cognitive examination and the brain MRI analysis with the SPM software provided the best performance on their own. The worst performing sources were typical parameters included in visual neuroradiological reporting, and the neurological examination. Overall, memory performance, genetic factors (like APOE and polygenic risk scores), and patters of atrophy in the entorhinal cortex, amygdala and hippocampus were the most important predictors."

POSTER N.º 32

Introduced by: Osta Pinzolas, Rosario

Title:

CLINICAL PARAMETERS ARE STRONG PROGNOSTIC FACTORS OF PROGRESSION TO DEMENTIA IN AN ELDERLY COHORT OF MCI PATIENTS.

Principal Investigator: Nora Molina Torres

Authors: Nora Molina Torres (1,2,3) | Carlos Platero Dueñas (4)| María Abadía Morales (5) | Laura Moreno Martínez (1,3) | Pol Andrés Benito (6)| Mónica Povedano Panades (6) | Oscar Pérez Berasategui (2) | Pilar Mesa Lampré (2) | Ana Cristina Calvo Royo (1,3) | Concepción de la Cámara Izquierdo (3,7) | Rosario Osta Pinzolas (1,3)

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Abstract:

“Introduction: Mild Cognitive Impairment (MCI) is a state between dementia and healthy ageing. This study describes the clinical features of a cohort of elderly patients and the role of p-tau 181 during disease progression. The prognostic role of cognitive, functional and frailty scales was also considered. Methods: This study was approved by the regional ethics comitee (CEICA, PI-19-455). This is a longitudinal prospective nested case-control study. Each patient had a first interview, and then two yearly interviews to monitor clinical progression. Patients performed neuropsychological and functional tests (MMSE, clock test, verbal fluidity, Barthel’s Index, Lawton’s Index, EURO-D). Patients over 70 years old were included if they matched the MCI International Working group criteria. P-tau 181, NFL, GFAP, abeta-40, abeta-42 and total-tau were measured in plasma samples from each patient (SIMOA by Quanterix). A Disease Progression Model (DPM) was designed to predict survival time. Results: 59 patients were included. Median age was 82,5+/-5,1; 68% of the sample were women. The patients were classified in a progression group (pMCI, 27 patients, 46%), and a cognitive stable group (sMCI, 32 patients, 54%). Depression was around 37% in both groups, and frailty was 50% (sMCI) vs 77%(pMCI). 57% patients had over 20 ng/ml of p-tau181. Of all clinical and molecular measures, only MMSE had prognostic value of progression from MCI to dementia. Conclusions: In a cohort of elderly MCI patients, MMSE has a strong prognostic value. P-tau 181 supported the etiological diagnosis of MCI, but it didn’t influence prognosis. “

POSTER N.º 33

Introduced by: Frades Payo, María Belén

Title:

CLINICAL FEATURES OF MIXED NEURODEGENERATIVE PATHOLOGIES IN AGING BRAINS

Principal Investigator: M. Belén Frades-Payo

Authors: M. Belén Frades-Payo1 ; E. Lucía Valeriano-Lorenzo1 ; Alberto Rábano 1,2 ; M. José López Martínez 1,2 ; Alicia Ruiz 1 ; Sonia Wagner 1 ; Nekane Moreno 1 ; Mario Ricciardi 1 ; M. Ascensión Zea1 ; Merixell Valentí1 ; Pascual Sánchez-Juan1 and Teodoro del Ser 1 .

Filiation: 1. Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain; 2., Clinical platform and Biobank, Madrid, Spain.

Abstract:

“ Objective: Analyze the impact of the association of multiple brain pathologies on cognitive function Methodology and Sample: Clinical and pathological data of 164 subjects (78% female; mean age at exitus: 87.3±6.7) with dementia and postmortem neuropathological study. The presence of Alzheimer disease lesions (AD), Lewy bodies (LB), TDP-43 deposits (LATE), small vessel lesions (SVL), argyrophilic grains (AG) and age-related tau astrogliopathy (ARTAG) was recorded, and quantified. The number of pathologies was correlated with cognitive performance (Severe MMSE, Semantic fluency), behavioral disturbances (NPI), functional (Barthel Index), and motor status (Tinetti) at baseline and ante-mortem, adjusting for age at the clinical onset of cognitive decline and sex. Findings: The higher number of pathologies is significantly associated with older age, longer clinical history and more brain atrophy. The number of pathologies is negatively and significantly correlated with cognitive performance functional and motor status both at baseline and at pre-morten assessments; however, it is not correlated with the changes during the observation period. Conclusions: The mixed pathology is very frequent and is associated with more extended age and duration of disease, with worse cognitive, functional and motor status at baseline and ante-mortem time, and with more brain atrophy. However, it does not determine a different clinical progression.

ABSTRACTS BOOK 2024

POSTER N.º 34

Introduced by: Castro Labrador, Sandra

Title:

THE EFFECT OF ALZHEIMER'S DISEASE CO-PATHOLOGY ON COGNITIVE PHENOTYPE AND FDG-PET PATTERNS IN PARKINSON'S DISEASE WITH COGNITIVE IMPAIRMENT

Principal Investigator: Sandra Castro-Labrador

Authors: Sandra Castro-Labrador1,2, Jesús Silva-Rodríguez1,2,3, Miguel Ángel Labrador-Espinosa2,3,,4, Laura Muñoz-Delgado2,3, Pablo Franco-Rosado2,3, Ana María Castellano-Guerrero2, Daniel Macías-García2,3, Silvia Jesús2,3, Astrid Adarmes-Gómez2,3, Elena Ojeda-Lepe2, Fátima Carrillo2,3, Juan Francisco Martín-Rodríguez2,3, San Eufrasio M. 2, Cristina Pérez-Calvo2, Nicholas J. Ashton4,5,6, Henrik Zetterberg5,6, Florinda Roldan Lora7, David García-Solís8, Pablo Mir2,3,9, Michel J. Grothe1,2,3

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Abstract:

"Objective: To explore how Alzheimer's disease (AD) co-pathology affects the pattern of cortical neurodegeneration in patients with Parkinson's disease (PD) and cognitive impairment (CI). We used plasma ptau217 to study the effect of AD co-pathology on APOE4 genotype, cognitive profile and cortical hypometabolism on FDG-PET in a well-characterized cohort of PD and CI patients. Methods: Eighty-eight PD patients were classified into PD-CI (N=50; 24 PD-MCI, 26 PDD) and PD with normal cognition (PD-CN; N=38) using neuropsychological testing with the PD-Cognitive Rating Scale. All underwent blood sampling and FDG-PET scanning. Plasma ptau217 levels were measured using the ALZpath ptau217 Simoa immunoassay, with a threshold of 0.4 pg/mL for ptau217 positivity. APOE4 alleles were genotyped and coded as a binary variable. FDG-PET data was processed using SPM12 and brain-wide hypometabolism patterns (vs PD-CN) were assessed across 52 atlas-defined brain regions. Results: Fourteen PD-CI (28%) and 5 PD-CN (13%) patients were classified as ptau217(+). PD-CN-ptau217(+) were excluded from further analysis. PD-CI-ptau217(+) patients showed a higher prevalence of APOE4 carriers (50% vs 16%, p=0.04) and more impaired memory scores (p=0.03). When compared to PD-CN, both PD-CI-ptau217(-) and PD-CI-ptau217(+) showed significant hypometabolism in posterior-occipital, temporal, and frontal areas ($p<0.05$, FDR-corrected), but hypometabolism in PD-CI-ptau217(+) was considerably more extensive, particularly in temporo-parietal areas. Conclusions: AD co-pathology results in a more memory-predominant cognitive profile and AD-like neurodegeneration phenotype in PD-CI. Novel plasma biomarkers may significantly facilitate clinical detection of AD co-pathology, which may have important implications for personalized diagnosis, prognosis, and treatment of PD patients.

POSTER N.º 35

Introduced by: Iláco, Maria Carolina

Title:

ACCURATE SEGMENTATION OF BRAIN REGIONS OF INTEREST IN [18F]FDG PET IMAGES TO IMPROVE QUANTITATIVE ASSESSMENT AND DIAGNOSIS OF NEURODEGENERATIVE DISEASES USING ARTIFICIAL INTELLIGENCE

Principal Investigator: Maria Carolina Iláco

Authors: Maria C. Iláco (1,2), Francisco Oliveira (1), Cláudia Constantino (1), José M. Fonseca (2), Durval C. Costa (1)

Filiation: 1 Nuclear Medicine - Radiopharmacology, Champalimaud Foundation, Lisbon, Portugal. 2 NOVA School of Science and Technology, NOVA University of Lisbon, Caparica, Portugal.

Abstract:
“Aim: Precise quantification of grey matter (GM) uptake of [18F]FDG helps in the differential diagnosis of neurodegenerative diseases. This study assesses the feasibility of using [18F]FDG PET images for automatically segmenting brain regions of interest (ROI) and its impact on [18F]FDG uptake quantification. Methods: The dataset comprises 264 subjects (cognitively normal, mild cognitive impairment, and Alzheimer’s disease) from the Alzheimer’s Disease Neuroimaging Initiative database. Each subject had both [18F]FDG PET and MRI scans. Two [18F]FDG PET segmentation methods were compared on 23 brain ROI: artificial intelligence-based (FDG-AI-based), and FDG-Atlas-based (standard approach). MRI-based segmentation was considered the gold standard. Segmentation performance was evaluated using a measure of overlap between segmentations – the Dice similarity coefficient (DSC). The agreement and/or correlation of the uptake quantification based on the different segmentation methods was assessed using the intraclass correlation coefficient (ICC) and Pearson correlation coefficient (r). Results: For the FDG-AI-based segmentation, the median DSC was 0.80, consistent across all subject groups and ROI (0.71≤DSC≤0.93). Agreement on the [18F]FDG GM uptake quantification using the FDG-AI-Based and MRI-based segmentation methods was excellent (0.89≤ICC≤1.00, 0.90≤r≤1.00), with mean absolute deviation of 2% (maximum 16%). Regarding the FDG-Atlas-based method, the quantification results were significantly inferiors (0.46<r<0.96) and less consistent among subjects’ groups. Conclusion: The FDG-AI-based segmentation method is reliable, originating more accurate quantifications than the standard FDG-Atlas-based quantification approach. Thus, it may improve diagnosis accuracy in clinical routine. However, further work is required to validate this method in other neurodegenerative diseases and with larger datasets.

POSTER N.º 36

Introduced by: Sánchez Martín, Cristina

Title:

SUBJECT-LEVEL DETECTION OF FOCAL NEURODEGENERATION USING SPATIOTEMPORAL CONNECTOMICS: TOWARDS ATROPHY CHARACTERIZATION IN PRECLINICAL ALZHEIMER'S DISEASE

Principal Investigator: Cristina Sánchez

Authors: Cristina Sánchez[1], Ibai Diez, PhD[2], Elisenda Bueichekú, PhD[3], Chan-Mi Kim, PhD[2], Michel J. Grothe,PhD[1], Pascual Sanchez-Juan, PhD, MD[1] and Jorge Sepulcre, MD, PhD[3],

Filiation: [1]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Madrid, Spain. [2]Gordon Center for Medical Imaging, Massachusetts General Hospital, Boston, MA, USA. [3]Yale University, New Haven, CT, USA.

Abstract:
"Background: Brain atrophy is a normal part of healthy aging, but it is aggravated by several neurodegenerative diseases. Previous studies have described heterogeneity in individual neurodegeneration patterns, but the underlying brain mechanisms are currently not fully understood. From a graph theory-based framework, the estimation of subject-specific focal or multifocal brain atrophy in healthy aging and in the preclinical stage of different neurodegenerative diseases, such as Alzheimer's disease, will help to better understand individual atrophy networks and likely improve prediction of phenotypic heterogeneity in disease trajectories. Method: The study included 78 older cognitively normal participants from the Vallecas project, who underwent longitudinal T1 MRI scanning with 8 follow-up timepoints. Voxel-wise gray matter volumes were obtained, and the topology of atrophy of each subject was defined. After that, we selected gray matter values with 1% annual decrease as accelerated atrophy measure. A graph theory approach based on the structural similarity of all pairs of voxels with accelerated atrophy was applied to identify uni- or multifocal atrophy patterns. Results: We identified individualized atrophy phenotypes based on the convergent or divergent behavior of voxels with accelerated atrophy, which in turn is characterized by different graph morphologies. Conclusions: We present a novel analytical tool for characterizing individualized atrophy phenotypes in healthy subjects based on graph theory and structural similarity analyses. This method may help to describe the first structural events in preclinical AD and other neurodegenerative diseases and, therefore, could be crucial for predicting differences in disease phenotype and progression in single subjects.

POSTER N.º 37

Introduced by: Uceda-Heras, Alicia

Title:

SYSTEMATIC VARIATION OF MYELIN ACROSS AREAS OF THE HUMAN TEMPORAL CORTEX OBSERVED ON MRI

Principal Investigator: Alicia Uceda-Heras

Authors: Alicia Uceda-Heras, Francisco J López-González, Linda Zhang, Jesús Silva, Alberto Rábano

Filiation: Reina Sofia Alzheimer Center,CIEN Foundation, BT-CIEN, ISCIII, Madrid, Spain

Abstract:

“The expression of synaptic plasticity markers varies systematically across cortical areas in primates, being lower in limbic areas, of poor laminar elaboration, and higher in eulaminate areas, with six-well developed layers. Selective vulnerability of temporal mesocortical areas has been observed in Alzheimer’s disease (AD), suggesting that simpler laminar architecture may be associated with the expression of factors that render mesocortical neurons more vulnerable than in eulaminate areas. Here, we present a simple manual method to quantify the intracortical content of myelin (well-known inhibitor of synaptic plasticity) along the cortex of the temporal lobe. To this end, we used T1-MRI coronal slices of 16 individuals from the Fundación CIEN Brain Bank, which were normalized with MatLab-SPM function and loaded in Image J. Intracortical myelin content was quantified by a ROI for each cortical type at 4 coronal levels of the temporal lobe, obtaining the mean-grey value of myelin. Our data show increased myelin density in eulaminate areas compared to limbic areas. The content of myelin also increased across eulaminate areas of progressively better laminar elaboration. These findings suggest that limbic areas of the human temporal cortex are more plastic than eulaminate temporal areas. Therefore, higher synaptic plasticity of limbic temporal areas may be related to the selective vulnerability to AD. Prospects for this project include the validation of these results within an extensive sample and comparing this method with automated methods, like the Lesion Segmentation Toolbox (LST)-AI-deep-learning-ensemble. Moreover, these results will be compared with histological post-mortem analysis of intracortical myelin. “

POSTER N.º 38

Introduced by: López González, Francisco Javier

Title:

CHOLINERGIC WHITE MATTER PATHWAYS IN ALZHEIMER'S DISEASE, DEMENTIA WITH LEWY BODIES, AND OTHER NEURODEGENERATIVE DISEASES: A POST-MORTEM MRI STUDY

Principal Investigator: Francisco J. López-González

Authors: Francisco J. López-González1, Milan Nemy2, Cene Jerele2,3, Alberto Rábano1, María José López Martínez1, Michel J. Grothe1, Pascual Sánchez-Juan1 and Daniel Ferreira2

Filiation: 1Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain 2Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden 3University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia

Abstract:
"Background: We propose an imaging-pathologic validation study aimed at investigating cholinergic WM pathways using post-mortem MRI of autopsy-confirmed AD, Lewy body dementia (LBD), mixed pathology (AD+LBD), other neurodegenerative diseases across the frontotemporal lobar degeneration (FTLD) spectrum (OD) and cognitively unimpaired donors (CU). Method: We included 55 brain donors (21 AD, 14 AD+LBD, 8 LBD, 7 OD and 5 CU). All donors underwent post-mortem MRI in situ and a neuropathological examination. Mean diffusivity (MD) maps were estimated using the FSL software for each donor and for two cholinergic WM pathways of interest: cingulum and external capsule. Moreover, regional cholinergic WM signal abnormalities were visually scored on FLAIR images using the Cholinergic Pathways HyperIntensities Scale (CHIPS). Differences in MD, CHIPS and in age-adjusted values/scores (after excluding the CU group) between groups were analysed using the Mann-Whitney U-test. Result: AD donors were older than LBD ($p=0.01$) and than OD ($p=0.02$); and CU donors are significatively younger than all other groups ($p<0.02$). AD and AD+LBD showed higher MD values in cholinergic WM pathways when compared with OD (Cohen's $d\geq0.5$, $p=0.05$) and LBD (Cohen's $d\geq1.3$, $p<0.01$). Qualitatively similar findings were obtained after adjusting for age but at lower effect size and statistical significance Conclusion: We confirmed the degeneration of cholinergic WM pathways in neuropathologically confirmed dementia groups. This degeneration is more severe in the AD groups than in the LBD group, possibly due to differences in the degree of disease/dementia severity. Additionally, DTI-based indices of cholinergic pathway integrity strongly correlate with CHIPS-based visual assessment.

POSTER N.º 39

Introduced by: Sacchini, Simona

Title:

NEURODEGENERATIVE DISEASES: WHAT CAN BE LEARNED FROM TOOTHED WHALES?

Principal Investigator: Simona Sacchini

Authors: Simona Sacchini

Filiation: Universidad de Las Palmas de Gran Canaria (ULPGC). Las Palmas de Gran Canaria, Spain

Abstract:

“Different studies have demonstrated neurodegeneration in animals, as marine mammals. The suborders Mysticeti (baleen whales) and Odontoceti (toothed whales) make up the entire order Cetacea. As “”sentinels”” of the marine environment, toothed whales top-predators can serve as useful models of diseases for their human counterpart. Recent studies have revealed that some marine mammals, as toothed whales, exhibit neuropathological traits that recapitulate an Alzheimer’s-like pathology and might help in improving our comprehension of the neurodegenerative disorders (Sacchini et al. 2020; Vacher et al. 2023; Garamszegi et al. 2024). On the other hand, “”selective neuronal vulnerability”” describes the characteristic of neurodegenerative diseases where the pathology is limited to certain neurons. Conversely, neuromelanin has unique characteristics in humans and primates that are not seen in other animals. Neuromelanin was firstly observed in several species of the family Delphinidae (Sacchini et al. 2018) and transmission electron microscopy revealed the existence of melanin granules linked to lipid droplets and membranes, that closely resembled human neuromelanin, in two toothed whales (Sacchini et al. 2022a). Finally α-synuclein, ubiquitin, and laforin have been checked in toothed whales (Sacchini et al. 2022b), and α-synuclein/ubiquitin immunopositive round bodies were found in the neuropil of the mesencephalon. The advantages of transgenic rats are indisputable, but alternative natural, non-transgenic models may yield more pertinent data on the physiopathology of neurodegenerative diseases. “

POSTER N.º 40

Introduced by: Ettcheto, Miren

Title:

B-CARYOPHYLLENE ENHANCES COGNITION AND REDUCES ALZHEIMER'S PATHOLOGY IN APPSWE/PS1DE9 MICE

Principal Investigator: Constanza Catalina Paz Rocha Jaures

Authors: Jaures CCPR1,2, Fernandes MJS1, Mourão RHV6, Guzman L2,3,4, Carrasco M2,3,4, Camins A2,3,4,5, Ettcheto M2,3,4,5

Filiation: 1. Department of Neurology and Neurosurgery, Discipline of Neuroscience, Federal University of São Paulo (UNIFESP), São Paulo, Brazil. 2. Department of Pharmacology, Toxicology, and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona (UB), Barcelona, Spain. 3. Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain. 4. Institute of Neuroscience, University of Barcelona, Barcelona, Spain. 5. Pere Virgili Health Institute (IISPV), Reus, Spain. 6. Laboratory of Experimental Biology and Bioprospecting - LabBBEx, Federal University of Western Pará (UFOPA), Santarém-Pará, Brazil.

Abstract:
"β-caryophyllene (BCP) is a terpene found in various plants and tree resin, known for its role in regulating inflammation and oxidative stress. As a phytocannabinoid, it is a potential drug for preventing neuroinflammatory and neurodegenerative diseases like Alzheimer's Disease (AD). AD is the most common form of dementia, characterized by beta-amyloid plaques, glial activation, neuronal death, and loss of synaptic function, leading to cognitive decline and memory loss. Therefore, this study aimed to assess whether BCP can inhibit key pathological mechanisms in a familial AD mouse model. For that, five-month-old female APPswe/PS1dE9 (APP) and wild type C57BL6/J (WT) mice were treated with BCP (48 mg/kg) or vehicle (VEH) intraperitoneally three times/week for four weeks. Cognitive function was evaluated using the Morris water maze (MWM) and novel object recognition test (NORT), while anxiety behavior was assessed with the open field (OF) test. Additionally, Aβ42 levels and dendritic spine density were measured. The results showed a significant improvement in learning and memory in APP mice treated with BCP compared to APP VEH. This cognitive improvement was associated with reduced dendritic spine loss in the hippocampus and decreased Aβ42 levels in the cortex. Furthermore, BCP treatment significantly reduced anxiety-like behavior in APP mice. In conclusion, BCP treatment enhanced cognition, reduced anxiety-like behavior, preserved dendritic spine density, and affected Aβ42 levels, demonstrating its potential neuroprotective benefits in AD. These findings suggest that BCP could help mitigate the progression of AD.

POSTER N.º 41

Introduced by: Sánchez, Juan

Title:

EXTRACELLULAR SPACE REMODELING CONTRIBUTIONS TO ADULT BRAIN REGENERATION.

Principal Investigator: Juan Andrés Sánchez

Authors: Sánchez JA1, Santos M1, Simões A1, Alves C1, Encinas JM2, Rhiner C1

Filiation: 1 Stem cell and Regeneration Laboratory, Champalimaud Foundation, Lisbon, Portugal. 2 Laboratory of Neural Stem Cells and Neurogenesis, Achucarro Basque Center for Neuroscience, Bizkaia, Spain.

Abstract:
The regenerative potential of the adult brain lies within the neural stem cells (NSCs), a group of dormant cells capable of generating new neurons and glial cells. The NSCs are embedded in dedicated environments that are composed of heterogeneous cells that cohesively remodel the extracellular space to promote the NSCs activation when it is needed. Poor activity in these niches has been associated with neurodegenerative disorders, including Parkinson and Alzheimer. However, how these specialized regions coordinate the emergence of new cells remain elusive and are the main focus of my research. Previously our group conducted a transcriptomic analysis to identify genes coding for extracellular proteins differentially expressed in the Drosophila brain upon injury. Interestingly we found that the gene CG14309, predicted to be a mammalian Heparanase orthologue, is activated at early time points and is necessary for proliferation upon acute injury in the Drosophila optic lobe. Whether CG14309 functions as a Heparane Sulfated Proteoglycan cleaving protein is still unknow and we hypothesize that it is important for extracellular matrix remodeling and promoting the activation of the quiescent NSCs. Simultaneously, we are generating a cell-cell interaction tracing system to identify and genetically modify the NSCs local environment. Overall, we are working to provide a detailed knowledge about cell interactions within the NSC niches by elucidating molecular and cellular mechanisms and ultimately a comprehensive framework for harnessing the latent regenerative capacity of the brain.

ABSTRACTS BOOK 2024

POSTER N.º 42

Introduced by: Serrano-Marín, Joan

Title:

NORMALISATION OF HUMAN TEAR METABOLOMICS DATA ALLOWING INTER-INDIVIDUAL COMPARISONS OF PATIENTS WITH NEURODEGENERATION

Principal Investigator: David Bernal-Casas

Authors: Joan Serrano-Marín1, Silvia Marín2,3,4, Alberto Iglesias1#, Jaume Lillo1,5*, Claudia Garrigós1, Toni Capó1, Irene Reyes-Resina5,6, Hanan Awad7, Marta Cascante2,3,4, Juan Sánchez-Navés8, Rafael Franco2,5,9, David Bernal-Casas10

Filiation: 1 Molecular Neurobiology Laboratory, Department of Biochemistry and Molecular Biomedicine, Universitat de Barcelona, Barcelona, Spain, 2 Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, Universitat de Barcelona (UB), Barcelona, Spain, 3 Institute of Biomedicine of University of Barcelona (IBUB), University of Barcelona (UB), Barcelona, Spain, 4 CIBEREHD, Network Center for Hepatic and Digestive Diseases, Spanish National Health Institute Carlos III (ISCIII), Madrid, Spain. 5 CiberNed, Network Center for Neurodegenerative Diseases, Spanish National Health Institute Carlos III (ISCIII), Madrid, Spain. 6. Department of Biochemistry and Physiology, Faculty of Pharmacy and Food Sciences, Universitat de Barcelona (UB), Barcelona, Spain, 7. Department of Optometry, College of Applied Medical Sciences, Qassim University, Almulida, Qassim, Saudi Arabia. 8 Department of Ophtalmology, Oftalmedic and I.P.O. Institute of Ophthalmology, Palma de Mallorca, Spain, 9 School of Chemistry, Universitat de Barcelona, Barcelona, Spain.

Abstract:
To allow meaningful inter-individual comparisons, this study introduces a new method for analyzing human tear data, known for its high variability in composition. Metabolomic data were used to predict the concentrations of metabolites based on the concentration of a single concomitant metabolite, the individual's age, sex, and fasting time. Central to this approach is the concept of precision medicine, acknowledging that each patient will have a unique tear composition. By combining our method with Linear Discriminant Analysis (LDA), we were able to accurately determine the sex of individuals based on just one metabolomic parameter in tear. Similarly, this development could lead to diagnosis or detection of trends in patients with neurodegenerative diseases using a parameter consisting of the concentration of a predetermined metabolite. This advancement demonstrates the potential for using human tears for diagnostic purposes, as our method allows for the use of tear composition to identify significant differences, including those related to sex. Our findings indicate that this approach could support the use of tear analysis in medical diagnostics, facilitating the identification of various physiological and pathological conditions through tear composition.

POSTER N.º 43

Introduced by: Nascimento, Marta

Title:

ALCOHOL RELATED DEMENTIA OR ALCOHOL RELATED BRAIN DAMAGE?

Principal Investigator: Marta Nascimento

Authors: “Marta Nascimento Liliana Pereira”

Filiation: Neurology department of Unidade de Saúde Local de Almada Seixal

Abstract:

“INTRODUCTION: Alcohol is a major preventable burden for global health. The association between alcohol use disorders and cognitive impairment has long been recognized in epidemiological studies. However, the role of alcohol as an etiological mechanism for dementia itself remains controversial. In fact, alcohol related brain damage is an umbrella for other common causes of cognitive impairment related to alcohol use such as: traumatic head injury, vascular risk factors, hepatic encephalopathy, nutritional deficiencies and psychiatric disorders. METHODS: Nonsystematic review of literature RESULTS: The amount and duration of alcohol consumption enough to cause alcohol related dementia (ARD) is unclear. Some authors, however, stress the drinking pattern, pointing features as binge drinking duration and withdrawal periods. Two lines of research seem to explain ARD: “Glutamatergic excitability” and “Thiamine deficiency”. Both could explain the potential for neuroinflammation and oxidative stress caused by alcohol. In order to stimulate research and to minimize the subjective clinical judgment, some authors proposed a set of criteria for “Probable” and “Possible” diagnosis of ARD. Characteristics of ARD include - presence of other alcohol-related organ damage, reversibility or stability of cognitive deficits and neuroimaging features, symptoms of cerebellar dysfunction and sensory neuropathy. The following do not favor ARD diagnosis: prominent language impairment, focal neurological signs, neuroimaging evidence of cerebrovascular disease or focal brain pathology. Diagnosis cannot be made before 60 days of alcohol abstinence. CONCLUSIONS: In the rising scene of dementia prevalence, knowledge of alcohol contribution for brain lesion may stimulate the development of more efficacious therapeutic and prevention strategies.

POSTER N.º 44

Introduced by: Franco, Rafael

Title:

VITACTIONS. VITAMINS FOR THE BRAIN

Principal Investigator: Rafael Franco

Authors: Rafael Franco

Filiation: 1. CiberNed. Centro de Investigación en Red, Enfermedades Neurodegenerativas. Instituto de Salud Carlos III. Madrid. Spain. 2. Depto. Bioquimica y Biomedicina Molecular. Universitat de Barcelona. Barcelona. Spain

Abstract:
"A novel concept has been recently put forward in the mind/body interface (https://doi.org/10.37349/ent.2024.00074). The new concept has led to a new word: vitaction. Vitactions offer benefits to the brain and mind comparable to the advantages vitamins provide for the body's overall health. The field of vitactions is as it was the vitamin field one century ago, i.e., without tools to make a complete classification. I propose to classify vitactions into five categories according to the behaviours necessary to maintain balanced brain functionality. A deficit of vitactions would contribute to the enormous prevalence in developed countries of diseases ranging from type 2 diabetes to neuropsychiatric diseases. The concept should help to identify which vitactions are deficient and to outline how they can be progressively implemented to improve the quality of life. The parallelism vitactions/vitamins also extends to overdosing; both hypervitaminosis and hypervitactinosis may be detrimental. This perspective article argues that vitactions should be considered at the practical and the scientific research levels, and that a balanced vitamin and vitaction supply is essential for a better life. In addition, reasons for proposing a synonym, "vitactin", are given. The article: Vitactions: vitamins for the brain is available at https://www.explorationpub.com/uploads/Article/A100484/100484.pdf