A combination of top-down and bottom-up approaches addressing the inverse occurrence of Alzheimer’s disease and cancer enables to classify patients based on their genotypes

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The inverse relationship of occurrence of Alzheimer’s disease (AD) and cancer has been reported in several population-based studies and meta-analyses. The different distribution of exposures to known risk factors in people with cancer or AD was found insufficient to explain, in our previous cohort study, the lower-than-expected co-occurrence. Therefore, we investigate the genetic basis underlying the inverse relationship by analyzing common genetic variants differently expressed in the two diseases. The study explores and identifies the genotypic “red flags” that could distinguish and classify a priori the AD and cancer cases. A comparative analysis explored the distribution of 545,982 known single nucleotide polymorphisms (SNPs) in the genome of large populations of cancers (N = 4,409) and AD (N = 1,292) patients from NIH dbGaP datasets. GWAS, PCA methods, SNPnexus, and ToppGene tools were employed to compare the datasets, to distinguish molecular processes associated with AD and cancer, and to select a set of SNPs differentially distributed in the two diseases. The GWAS analyses identified 300 SNPs (p < 10⁻⁵) associated with 213 unique genes (SNPnexus functional annotation). The gene set enrichment analysis (GSE) in ToppGene identified 11 out of 213 genes as significantly (p < 10⁻⁵) enriched for phospholipid binding (GO:0005543): ABCA1, CADPS, GBF1, KCNQ1, MARCKS, NFI, PLD1, PKX, SNX29, TIAM1, ZFYVE26. Furthermore we tested the SNPs’ ability to discriminate AD form cancer cases by means of contingency tables and a receiver operating characteristic (ROC) analysis. ROC score performance resulted high (AUC = 72.9) for 11 most significant SNPs from the GWAS analysis, while 11 SNPs associated with the phospholipid binding even better classified AD vs. cancer cases (AUC = 78.1). The adopted combination of top-down and bottom-up approaches indicates its potential explanatory capabilities. These preliminary results show that genes, identified by SNPs significantly different in the two diseases, are involved in shared biological pathways that, if deregulated, may explain the divergent trajectories towards AD or cancer. The differentially distributed SNPs might have potential clinical applications that could direct future research. Further investigations using other independent genetic datasets are required to confirm these findings that, if successfully replicated in silico, can form the basis for specific in vitro and in vivo studies on the inverse occurrence of the two diseases.
Clinico-pathological correlates in a patient with atypical dementia and multiple cerebral proteinoses

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Objectives: To report a peculiar case of atypical dementia associated with multiple cerebral proteinoses. Materials and methods: Case report: A 62-years-old woman with positive family history for dementia presented with behavioral changes, mild attention deficits, and amnesic disturbances. Two years later, the diagnosis of amnestic MCI associated with behavior changes was made, and AChEI therapy slightly improved the amnesic deficit. After 2 years, a progressive extrapyramidal syndrome with rigidity, bradykinesia, and frequent falls sensitive to levodopa therapy was made, and the patient presented with behavioral changes, mild attention deficits, and amnesic disturbances. Two years later, the diagnosis of disease continued to rapidly worsen also because of the occurrence of cerebellar atrophy, prevalent at frontal and temporal lobes, and atrophy of mesencephalon. CSF examination showed increased tau protein (951 pg/mL), and positive 14-3-3 protein. No mutations were found in tau and progranulin genes. The neurological condition continued to rapidly worsen also because of the occurrence of repeated subdural hemorrages. The patient died 6 years from the onset of disease. Neuropathology: in the cerebral cortex, severe neuronal loss and marked reactive gliosis was associated with numerous Aβ-amyloid deposits and congophilic angiopathy. Aβ deposits were also present in the caudate nucleus, putamen, thalamus, and cerebellum. In the mesial temporal structures, and several neocortical regions, neurofibrillary tangles (NFT) and neuropil threads were evident (Braak stage IV). In the pigmented nuclei of the brainstem and in the cerebral cortex, in particular in the temporal areas, the immuno-nostaining with anti-α-synuclein antibodies showed numerous Lewy bodies and neurites (Braak stage V). Globular NFT were numerous in the locus coeruleus and in the reticular formation of the pons and medulla. In the cerebral cortex and in the subcortical white matter, especially in the frontal lobes, caudate nucleus, and putamen, tufted astrocytes and coiled bodies intensively immunoreactive for phosphorylated tau were present. Immunohistochemical staining for phosphorylated prion protein was negative.

Conclusion: This case shows the concurrence of multiple cerebral proteinoses that correlate with the unusual clinical features of atypical dementia. The coexistence of three pathologic conditions, Alzheimer’s disease, dementia with Lewy bodies, and progressive supranuclear palsy, raises the question of possible common pathogenetic mechanisms favoring multiple types of protein change in conformation in the brain.

3D hydrogel-based cell model assays in MINERVA, a microfluidic organ-on-chip-engineered platform of gut-brain axis to study neurodegeneration

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Introduction: The bidirectional communication between gut and brain has been implicated in neurodegeneration, including Parkinson’s disease (PD). In fact, dysregulation of the brain-gut-microbiota axis may be associated with gastrointestinal signs frequently preceding motor symptoms. Gut-brain connection is based also on microbial neuroactive compounds and may explain a relationship among the microbiota, gut, and brain. MINERVA is an ERC project that aims at developing the first engineered microbiota-gut-brain platform. This will be based on serial organ-on-chip miniaturized microfluidic devices simulating the intestinal microbiota, the gut epithelium, the immune system, the blood-brain barrier, and the brain. To better recapitulate the physiologic condition, we are developing cell models in a 3D environment made by biosynthetic hydrogel-based materials. Here, we present the preliminary results about biocompatibility of hydrogel-matrices in cell models of gut and brain to be used in MINERVA. Material and method: Biocompatibility of collagen (COLL)/polyethylene-glycol (PEG) and COLL/hyaluronic acid (HA) have been tested with: primary cortical neurons from postnatal mouse (relevant for Alzheimer’s disease (AD)) and primary dopaminergic mesencephalic neurons from embryos (relevant for PD); neuroglioma cells (H4-SW), a model of AD expressing the Swedish mutant of the amyloid precursor protein (APP), and human epithelial colorectal adenocarcinoma cells (Caco2) as a model of gut epithelium. We tested two cell-hydrogel arrangements, hydrogel overlay and 3D embedding, the latter with increasing thickness (1.25, 2.5, and 3.95 mm). Cell viability was evaluated by MTS assay, while oligomer/fibril formation showed that 3.95 mm PEG/COLL and COLL/COLL seemed to stop their growth trend. Caco2 cell experiments showed that 3.95 mm PEG/COLL or HA/COLL seemed to stop their growth; otherwise, with 1.25 and 2.5 mm the growth trend was improved with HA/COLL during 14 days of test. Discussion and conclusion: The proposed COLL/H4 and COLL/PEG hydrogel matrix are potential candidates to be further investigated for 3D brain cell models recapitulating key features of AD or PD.
and gut model development. Finally, to improve the model, additional materials will be formulated and tested for mimicking human intestinal mucus, and iP cells (iDopaNeurons) will be tested for biocompatibility. MINERVA project has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation program (grant agreement N° 724734).

Retinal involvement in human prion diseases: neurophysiological and neuropathological study

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Aim: In prion diseases, pathological PrP deposition primarily involves the brain. Few studies have been performed, and conflicting results have been obtained about ocular tissue involvement in human prion diseases.

Material: Between 1997 and 2013, we observed 122 patients with the diagnosis of CJD according to the WHO criteria: 79 patients were classified as probable CJD, 43 as definite CJD based on the neuropathological analysis of the brain (29 patients) and/or the presence of PRPN gene mutations (20 patients). In 14 of the 29 patients that underwent autopsy, retinal tissue was collected. Methods: All patients were studied using an electroretinogram (ERG): a- and b-wave latency and amplitude, flicker 30 Hz, oscillatory potentials (OP) were recorded. Visual evoked potentials (VEP) analysis (latency and amplitude of P1, latencies of N1 and P2 and N1-P2 peak-peak amplitude) were also performed. Retinal samples were collected at autopsy, then fixed for histological and immunohistochemical studies for pathological PrP by means of 3F4 monoclonal antibodies or frozen for biochemical analysis. Results: ERGs/VEPs were abnormal in over 60% of CJD patients: the a-wave has been relatively spared, while the b-wave, latency and amplitude, the flicker 30 Hz, and the OPs revealed definite changes in some pattern and under definite condition. VEP did not show significant alteration compared to controls. Pathological PrP was present in all the 14 retina samples of CJD patients examined. Discussion and conclusion: ERGs/VEPs revealed abnormalities in a consistent ratio of CJD patients. The presence of pathological PrP in the retina is a very consistent finding in all types of CJD. No correlations were found between the pattern of PrP deposition in the retina and codon 129 polymorphism of PRNP, type of pathological PrP present in the brain, and disease duration.

Clinical and morphological features of two cases with myotilinopathy and desminopathy

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Objectives: Myofibrillar myopathies (MFM) are a group of morphologically homogeneous and genetically heterogeneous neuromuscular disorders, associated with a wide phenotypic spectrum. The morphologic changes in skeletal muscle in MFM are characterized by disintegration of the sarcomeric Z disc and myofibrils and by abnormal ectopic accumulation of multiple proteins involved in the structure of the Z disc. Case description: Case 1, female, 73 years old. Since the age of 70, she complained of progressive axial muscle weakness (bent syndrome). She reported a previous therapy with statins for 15 years. Blood CK was 500 U/L. Muscle MRI showed a diffuse fat infiltration of the lower limb. Cardiac and respiratory evaluation was normal. A family history of muscle diseases was not reported. Case 2, male 37 years old. Since the age of 28, he complained of a progressive pelvic girdle weakness with difficulties in climbing stairs and rising from sitting or supine position. Neurological examination also showed bilateral ptosis and mild rhinolalia. Blood CK was 500 – 600 U/L. His cardiac and respiratory evaluation was normal. Notably, his mother was diagnosed with “myositis”, and she died of sudden death at the age of 33 years. The muscle biopsies of both cases showed several fibers with clear vacuoles in sections stained with hematoxylin and eosin and Gomori-modified trichrome. Vacuoles had an oval shape or lobulated border. Ultrastructural analysis confirmed disintegration of the sarcomeric Z disc and myofibrils. We hypothesized a diagnosis of MFM. Next-generation sequencing analysis of genes associated with MFM detected respectively a pathogenic variant in MYOT gene and DES gene. Case 1 presented the c.179C>T heterozygous variant in exon 2 of the MYOT gene, resulting in the p.(Ser60Phe) substitution in the hydrophobic stretch of the protein. In case 2, the c.1255C>T heterozygous variant in exon 7 of the DES gene was identified, resulting in the p.(Pro419Ser) substitution in the tail region of the protein.

Beyond neurodegeneration: tau mutations as a novel risk factor for cancer

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