DIFFERENTIAL SIALYATION OF SERPIN A1, DETECTED BY NANOSCALE CAPILLARY ISOELECTRIC FOCUSING IN CEREBROSPINAL FLUID, AS AN EARLY DIAGNOSTIC MARKER OF PARKINSON’S DISEASE DEMENTIA

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Background: About 30% of patients with Parkinson’s disease (PD) develop a dementia in the course of the disease, called Parkinson’s disease dementia (PDD). Up to date, diagnosis of PDD is merely done by clinical parameters. Recently, we described by using two dimensional gel electrophoresis (2D and 2D immunoblot) that isoforms of the serine protease inhibitor Serpin A1 are differently sialylated in the cerebrospinal fluid (CSF) of healthy individuals and PD compared to PDD. However, 2D electrophoresis is time-consuming and cannot be used as a high-throughput approach.

Methods: We adopted a new nanoscale capillary isoelectric focusing (CIEF) approach for the detection of differentially sialylated Serpin A1 isoforms and compared this method to our former 2D immunoblot method. For this approach we used 50 patients with PDD, PD and non-demented controls. Results: 2D immunoblots gave mainly similar results like the CIEF approach. There was a significant difference in spot pattern between PDD, PD and CON. By CIEF we are now able to analyse up to 80 samples per day compared to 4-8 samples by our 2D immunoblot method.

Conclusions: The detection of different Serpin A1 isoforms by CIEF is rapid, sensitive and allows a large scale analysis of biosamples.

NITRO-PROTEOMICS TO DISCOVER SYNAPTOSOMAL BIOMARKERS OF NEUROINFLAMMATION IN ALZHEIMER’S DISEASE

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Background: Alzheimer’s disease (AD) is the most common neurodegenerative disorder causing irreversible, progressive dementia. AD is pathologically characterized by the presence of senile plaques, neurofibrillary tangles, and synapse loss. The interaction between synaptic proteins controls functions of learning, and memory. Loss of synaptic function has been shown to be an early pathogenesis event of AD. Post-translational modifications regulates nearly all aspect of synaptic function. It has been shown that nitric oxide and NO-derived molecules mediate post-translational modifications such as nitration and S-nitrosylation in AD. Increased levels of nitrated proteins have been reported in AD brain and CSF, suggesting a potential for disease pathogenesis. The pathologic processes of AD start decades before the onset of clinical symptoms. Thus early diagnosis with biomarkers may provide means of early disease detection. Methods: Globally analyze nitrotyrosine and S-nitrosylation in proteins of the synaptosome fraction using proteomic method. Male APP/PS1 mice age 3 and 9 months old are used as model of AD and healthy control male mice with the same age as a comparison for proteomic analysis. Fresh whole brain excluding the cerebellum and brain stem is used for synaptosome preparation. All samples are being analyzed using one-dimensional SDS PAGE and two-dimensional differential gel electrophoresis (2D-DIGE). Modified biotin switch technique is used for S-nitrosylation detection. Selected proteins will be validated as biomarker candidates in CSF or brain samples of patients with diagnosed mild cognitive impairment or AD. Results: Immunoblots of synaptosomal fraction from APP/PS1 mice showed increase of nitrosylated and nitrated proteins in several 1D-PAGE bands. Differentially modified proteins will be identified by establishing a Nitro-2D-DIGE workflow and mass spectrometry. Conclusions: Enhanced nitrosylation of proteins in synaptosomal fractions of APP/PS1 mice points to increased neuroinflammation as a potential source for nitric oxide. Identification of the modified proteins will establish a link between post translational modification of synaptic proteins and AD.

EVALUATION OF INCIDENCE AND CLINICAL FEATURES OF ANTIBODY-ASSOCIATED AUTOIMMUNE ENCEPHALITIS MIMICKING DEMENTIA

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Background: Paraneoplastic or non-paraneoplastic limbic encephalitis is an autoimmune disorder, presenting with acute/subacute onset, monophasic disease course and unique clinical findings. Alternatively, some limbic encephalitis cases may present with progressive dementia and behavioral symptoms mimicking chronic neurological or psychiatric disorders, emphasizing the importance of setting clinical criteria for selection of patients that require anti-neuronal antibody screening. Reported clinical features suggesting autoimmune encephalitis include a subacute onset with a rapidly progressive, often fluctuating course and inflammatory cerebrospinal fluid findings. Methods: Fifty consecutive patients fulfilling the clinical criteria for primary dementia, 130 control patients and 50 healthy controls were included. Their sera were investigated for several ion channel and glutamic acid decarboxylase (GAD) antibodies by a cell-based assay, radioimmunoassay and ELISA, as required.

Results: Sixteen patients satisfying dementia criteria had atypical findings or findings suggestive of autoimmune encephalitis. N-methyl-D-aspartate (NMDA) receptor antibody was detected in a patient with dementia, parkinsonism and REM sleep behavior disorder (RBD) fulfilling the criteria for dementia with Lewy bodies (DLB). One control patient with bipolar disease displayed low anti-GAD antibody levels. Conclusions: Our study showed for the first time the presence of parkinsonism and RBD in an anti-NMDAR encephalitis patient mimicking DLB. Although autoimmune encephalitis patients may occasionally present with cognitive decline, most dementia patients do not exhibit anti-neuronal antibodies, suggesting that routine analysis of these antibodies in dementia is not mandatory, even though they display atypical features.

DISTINCT BLOOD PROTEIN MARKERS ARE ASSOCIATED WITH BRAIN REGIONS OF EARLY AMYLOID DEPOSITION IN ALZHEIMER’S DISEASE

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Background: A key pathological hallmark of Alzheimer’s disease (AD) is the deposition of b -amyloid in the brain. There is a strong association between brain amyloid burden and the risk of developing AD-like