baseline BMP does not appear to have prognostic utility for PD progression.

1345

Changes in the level of glial neurotrophic factor in Parkinson's disease depending on the form

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Objective: To study the level of glial neurotrophic disease in blood plasma in patients with Parkinson's disease (PD) depending on the form.

Background: Neurotrophic factors (NF) are polypeptide compounds that are synthesized by neurons and glial cells and are involved in regulating the growth process.

Methods: A total of 88 patients were screened to assess the role and importance of glial neurotrophic factor in the early detection of Parkinson's disease. 78 patients with PC disease and 10 patients who did not have PC disease in the control group. Of the patients examined in the main group, 39 (50%) were men and 39 (50%) were women. Accordingly, the control group consisted of 5 men (50%) men and 5 women (50%). The average age of male patients with PC was 18-70 years, with an average age of 52.6 ± 11.1 years, and the average age of women was 32-68 years, with an average age of 59.7 ± 10.9 years. The duration of the disease was 4.1 ± 5.6 years in men and 6.32 ± 5.8 years in women. GDNF levels were determined by enzyme immunoassay.

Results: The results of measurements were obtained that in the blood serum of patients of the main group, the amount of glial neurotic inflammation was 34.655±7.5 pg/ml, in the control group 73.558±8.2 pg/ml, ($p<0.05$). In the next phase of the study, we found it necessary to perform a comparative analysis of serum GDNF in patients with various clinical forms of PC. The results show that the amount of GDNF in the akinetic rigid form is 35.5 ± 4.8 pg / ml, in the vibratory form of the disease - 31.5 ± 5.7 pg / ml, and in the vibratory form of the disease - 30.21 ± 4.8 pg / ml., in the mixed form of the disease was 28.2 ± 4.8 pg / ml, while in the early stages of the disease in 25 patients this figure was 38.2 ± 6.7 pg / ml.

Conclusions: A decrease of glial neurotrophic factor in the early stages of the disease indicates the onset of degeneration of dopaminergic neurons. Begins to decrease along the series of akinetic-rigid, tremor and mixed forms.

1346

Level of glial neurotrophic factor in the blood plasma depending on the duration of Parkinson's disease

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Objective: To study the level of glial neurotrophic factor in the blood plasma depending on the duration of PD.

Background: Study of the biochemical aspects of Parkinson's disease (PD) is an actual problem of modern neurology.

Methods: The material of this study was 78 patients with of PD. Duration of the disease – is 0.5 to 7 years. The control group consisted of 10 patients without symptoms of PD. Determines the content of glial neurotrophic factor in the blood serum by enzyme immunoassay performed with specific test systems developed on the basis of appropriate monoclonal antibodies on the analyzer Hospitex Diagnostics, Italy according to the instructions supplied with the kit.

Results: The results show that if the duration of 6-7 year, the level of glial neurotrophic factor in the blood plasma was 25,12 pg/ml, if the duration of 4-5 year, the level of glial neurotrophic factor was 32,65 pg/ml and in the duration 2-4 years the level of glial neurotrophic factor was 45,35 pg/ml, and in the control group the level of protein in blood plasma was 73.558±8.2 pg/ml. The level of glial neurotrophic factor in the blood plasma of PD is dependent on the degree of neurodegeneration. Patients with Parkinson's disease have a relatively high level of glial neurotrophic factor in the serum in the early stages of the disease.

Conclusions: The level of glial neurotrophic factor in the blood plasma of PD does not only depend on the clinical manifestations, and also depends on the duration of the disease.

1347 – Withdrawn

1348

The Vall d'Hebron Initiative for Parkinson (VHIP) cohort: a prospective, longitudinal and observational study enrolling de novo Parkinson's disease (PD) patients and carriers of PD-linked mutations for biomarker and pathophysiology studies

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Objective: To describe the study protocol of the Vall d'Hebron Initiative for Parkinson (VHIP) cohort, a prospective, longitudinal and observational cohort study aimed at deeply phenotyping de novo PD patients and carriers of PD-linked mutations. We anticipate this initiative will contribute to identify biomarkers for PD risk, diagnosis and prognosis, as well as to stratify disease subtypes and increase our understanding of pathophysiology at early PD stages.

Background: PD is a progressive neurodegenerative disorder causing a variety of motor and non-motor symptoms. To date, no disease-modifying treatment exists and diagnosis is based on the manifestation of the clinical motor symptoms, which occurs when the neurodegenerative process is already advanced. Studies designed to find diagnostic/prognostic biomarkers and pathophysiological pathways involved in disease onset/progression are needed.

Methods: Participants involving 150 de novo subjects and 150 aged- and sex-matched healthy controls are estimated to be recruited by the movement disorders specialists at the Vall d'Hebron University Hospital (Barcelona). After informed consent, subjects are evaluated to primarily assess objectives within four major domains of PD: motor, cognitive-affective, autonomic function and vision. First, an extensive clinical evaluation is performed by (i) recording demographic, personal history, lifestyle and dietary habits, and by (ii) completing clinical scales covering motor and non-motor symptoms. Second, data from autonomic function and visual function tests, together with neuroimaging data, are acquired. Finally, a wide range of biospecimens such as blood, cerebrospinal fluid, urine, feces, oral and olfactory mucosa, and skin biopsy are collected for biochemical and molecular assessments, including the genotyping of all participants. Participants will receive follow-up assessments at 2.5 and 5-year intervals.

Results: VHIP is the first study to establish a Spanish cohort combining clinical, imaging, biochemical and molecular data in de novo patients and PD-linked mutation carriers over time.

Conclusions: VHIP provides a unique opportunity to link pre-diagnosis disturbances to PD development, as well as to identify risk, diagnosis and prognosis biomarkers.

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Long non-coding RNAs in Parkinson's disease: bringing back life to the grey matter?

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Objective: Our study aims to discover and delineate the role of novel long non-coding RNAs (lncRNAs) in Parkinson's disease (PD).

Background: LncRNAs have been widely known to play important roles in the progression of several debilitating diseases such cancers, cardiovascular and neurological diseases. They can regulate gene expression transcriptionally or post-transcriptionally via several mechanisms. They can also be detected in bodily fluids and be used as biomarkers to improve diagnosis and prognosis of several diseases. Despite recent advances in the field, currently no lncRNA (or RNA) based biomarkers are available for the diagnosis or treatment of PD. In this study, we aim to discover novel lncRNAs possessing biomarker potential and delineate their role in PD.

Methods: a. LncRNA candidates were mined using publicly available RNAseq datasets from PD, non- PD and control derived neuron samples.

b. Promising lncRNA candidates were measured using qPCR in SH-SY5Y cells treated with 2mM MPP^+ for 24 and 48 hours to mimic parkinsonism.

c. Over-expression experiments for a lncRNA candidate were performed in order to uncover its function during PD pathogenesis via qPCR and western blotting.

DCFH-DA, respectively. Western blotting was performed to determine the levels of mitochondrial apoptotic markers such as Bax, Bcl2, and cleaved caspase-3, as well as HSP70 and heat shock factor-1 (HSF1).

Results: Melatonin reduced the MPP+-induced loss of cell viability [figure1] and levels of intracellular ROS [figure2] and mitochondrial apoptotic signaling proteins [figure3]. RA-differentiated SH-SY5Y cells exposed to melatonin and MPP+ exhibited increased expression of HSP70 and HSF1 with those exposed to MPP+ alone [figure4]. However, siRNA-mediated downregulation of HSF1 significantly attenuated the protective effects introduced by melatonin in the MPP+-induced PD model [figure5].

Conclusions: Our findings revealed the protective roles of melatonin in a model of PD pathogenesis. Melatonin can rescue the toxic effects of MPP+ on dopaminergic neuronal cell death via upregulation of the HSF1/HSP70 pathway. Further experimental studies would verify the therapeutic relevance of melatonin in association with HSP70 and HSF1 partners for the prevention and deceleration of PD-like neurodegeneration.

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Blood-derived α-synuclein from Parkinson´s disease patients is able to seed pathology

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Objective: To identify seeding capacities of soluble α-synuclein (α-syn) conformers derived from neuronal extracellular vesicles (NEs) from Parkinson´s disease (PD) patients.

Background: PD pathology is characterized by the aggregation of the synaptic protein α-syn that is able to form toxic oligomers as well as insoluble amyloid fibrils and causes cell death of neurons. These pathological conformers can be transmitted from cell to cell and are able to induce physiological, monomeric α-syn to form also pathological structures (prion-like propagation of protein misfolding and aggregation).

Methods: We studied 30 PD patients and 50 controls from our in- and outpatient clinic. After clinical examination and blood collection, extracellular vesicles were isolated from blood plasma. Next, neuron-derived extracellular vesicles (NEs) were purified from the total of vesicles. In subsequent analyses we performed α-syn amplification assays using PD- and control-NEs to study potential seeding capacities of soluble NE-derived α-syn from PD patients and controls. Seeding assay end products were validated by immunoblots and transmission electron microscopy.

Results: For all 30 PD patients seeding of pathological protein folding could be demonstrated, whereas no seeding capacities were detected in the control cohort. Amplified α-syn conformers were visualized by transmission electron microscopy and showed fibrillary appearance. Using structure-specific antibodies, raised against amyloid epitopes of protein aggregates, significantly increased signal intensities were detected in seeding assay end products of PD-NEs.

Conclusions: We show that the amplification of pathological neuronal α-syn conformers is possible and demonstrate that the ability to trigger α-syn seeding has the potential for a reliable blood biomarker of PD pathology. Further studies should validate these findings.

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Increased alpha-synuclein level in primary macrophages derived from patients with Parkinson's disease

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Objective: To assess glucocerebrosidase and alpha-synuclein level in primary macrophages derived from patients with Parkinson's disease with and without *GBA1* mutation.

Background: Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by the accumulation of abnormal protein aggregates of alpha-synuclein in the brain. Mutations in the *GBA1* gene, encoding the lysosomal enzyme glucocerebrosidase (GCase), are the most common genetic risk factor for PD. GCase is the key enzyme in ceramide metabolism, the enzyme hyderolyzes glucose moieties from glucosylceramide and glucosylsphingosine. Some studies demonstrated that reduced GCase activity might be resulted in increased alpha-synuclein protein. Monocyte-derived macrophages represent one of the most promising models for investigating molecular mechanisms of GCase dysfunction, as this cell type is vulnerable for disturbances in ceramide metabolism.

Methods: Mononuclear fraction was isolated from whole blood of patients with *GBA1* mutation with (GBA1-PD) (N=10), sporadic PD (sPD) (N=12) and controls (N=25). Primary macrophages were cultured using RPMI-1640 supplemented with 10% FBS, 1% gentamicin and 10 ng/ml M-CSF for 4 days, with daily media changes. Total protein (10μg) was separated by SDS-PAGE and then transferred to PVDF membranes by electroblotting. Primary anti-GBA and anti-GAPDH antibodies were used. Digital images were obtained by the chemiluminescence system ChemiDoc. Alpha-synuclein level was determined by ELISA using Human alpha-synuclein ELISA kit (Thermo Fisher Scientific, USA).

Results: In present study we showed an increased alpha-synuclein level in primary macrophages from GBA1-PD 1,14 (0,27 – 5,99) ng/μg and sPD patients 2,34 (0,37 – 4,61) ng/μg compared to controls 0,41 (0,09 – 1,60) ($p=0.005$, $p<0.001$, corresponding). Moreover, a decreased relative GCase protein level was observed in sPD primary macrophages 0,78 (-0,09 – 1,85) compared to controls 1,82 (0,46–3,74) ($p=0.025$).

Conclusions: Patients with Parkinson's disease are characterized by increased alpha-synuclein protein level in primary macrophages regardless of the status of the *GBA1* mutations. It is interesting to note that decreased relative GCase level in sPD patients may be triggered by the accumulation of alpha-synuclein.

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The overexpression of a-SYN leads to a differential process of mitophagy in neurons and atrocytes

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Objective: To determine the role of the different mitophagy pathways involved in PD, a key question that is still unresolved. We will investigate whether a-synuclein (α-SYN) WT and with the A53T mutation can modulate (induce/repress) mitophagy in neurons and astrocytes *in vivo* and *in vitro*.

Background: Mitochondria are organelles that perform essential functions in cells regulating metabolism, reactive oxygen species generation, and most importantly the production of most of its energy. Mitophagy is a quality control pathway whereby mitochondria are specifically targeted by autophagosomes for degradation within lysosomes. Mitochondrial dysfunction is a well-established pathological hallmark of Parkinson's disease (PD), probably due the high dependence on mitochondrial metabolism of neurons. However, whether mitophagy is altered in this disease is still a matter of intense debate.

Methods: We will assess mitophagy *in vivo* in MitoQC reporter mice after stereological injections of WT and mutated A53T α-SYN adeno-associated expression vectors. Along with mitophagy assessment, other mitochondrial parameters will also be evaluated to characterize mitostasis. Similar *in vitro* analysis will be performed in N2a cells that constitutively express α-SYN or immortalized astrocyte cell line (IMA2.1) treated with recombinant α-SYN.

Results: Results showed that *in vivo* α-SYN-WT or α-SYN-A53T neuronal overexpression leads to a decreased mitophagy in dopaminergic neurons of SNpc, whereas increased mitophagy occurs in reactive astrocytes surrounding area. *In vitro*, N2a expressing α-SYN showed increased mRNA expression of PINK1/PARKIN while reducing the expression of BNIP3/NIX, indicating the involvement of different mitophagy pathways.

Conclusions: Our results indicate that α-SYN (WT or A53T) overexpression induces differentiated mitophagy mechanisms between neurons and astrocytes, key for the development of PD.

1365

Glial neurotrophic factor as an early diagnostic marker in Parkinson's disease

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Objective: To study the level of glial neurotrophic disease in blood plasma in patients with Parkinson's disease (PD).

Background: Glial neutrophic factor (GDNF) is a random fact of a trophic neuron, especially dopaminergic neurons.

Methods: We examined 78 patients with PD aged 18 to 70 years (mean age 56.04±8.7), including 39 men and 39 women. The control group of patients included 12 patients without PD, who matched in age and sex. The duration of the disease was 4.1±5.6 years. All patients with clinical-neurological, neurophysiological and allergenic studies from patients with secondary brain diseases. GDNF levels were determined by enzyme immunoassay.

Results: The results of measurements were obtained that in the blood serum of patients of the main group, the amount of glial neurotic inflammation was 34.655±7.5 pg/ml, in the control group 73.558±8.2 pg/ml, ($p<0.05$). In the main content of the GDNF group, it was two times lower than in the control group. In patients with initial manifestations of PD, the GDNF level was 45.9±4.8 pg/ml, while in patients with a disease duration of 2-4 years, the GDNF level was 29.6±3.02 pg/ml, ($p<0.05$). A decrease for GDNF in the blood serum in patients with PD is associated with trophic of dopaminergic neurons in disorders of the pallidar system that occur in astrocytes cells.

Conclusions: Thus, based on the data obtained, it can be concluded that glial neurotrophic factor may be an early diagnostic marker of Parkinson's disease.

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The level of glial neurotrophic factor in blood plasma depending on the stage of Parkinson's disease

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Objective: To study the level of glial neurotrophic disease in blood plasma in patients with Parkinson's disease (PD) depending on the stage.

Background: Parkinson's disease (PD), along with other neurodegenerative diseases of the nervous system, is one of the most pressing socio-economic problems today and is one of the main causes of disability.

Methods: A total of 88 patients were screened to assess the role and importance of glial neurotrophic factor in the early detection of Parkinson's disease. 78 patients with PD and 10 patients who did not have PD in the control group. Of the patients examined in the main group, 39 (50%) were men and 39 (50%) were women. Accordingly, the control group consisted of 5 men (50%) men and 5 women (50%). The average age of male patients with PD was 18-70 years, with an average age of 52.6 ± 11.1 years, and the average age of women was 32-68 years, with an average age of 59.7±10.9 years. The duration of the disease was 4.1 ± 5.6 years in men and 6.32 ± 5.8 years in women. GDNF levels were determined by enzyme immunoassay.

Results: The results of measurements were obtained that in the blood serum of patients of the main group, the amount of glial neurotic inflammation was 34.655±7.5 pg/ml, in the control group 73.558±8.2 pg/ml, ($p<0.05$). In the next phase of the study, we found it necessary to perform a comparative analysis of serum GDNF in patients with various stage of PD. The results show that the amount of GDNF in the 1-stage is 26,3±4,9 pg / ml, in the 2-stage of the disease - 21,7±4,1 pg/ml, and in the 3-stage of the disease - 16,6±3,5 pg / ml, while in the early stages of the disease in 25 patients this figure was 38.2 ± 6.7 pg / ml.

Conclusions: The results obtained can be explained by the fact that the glial neurotrophic factor is specific to the astrocytic glia and is the main factor that nourishes the dopaminergic neurons. Begins to decrease along the series of 1-stage, 2-stage and 3-stage.

1367

Analyzing the metabolic function of DJ-1 in the pathogenesis of Parkinson`s disease (PD) and Glioblastoma multiforme (GBM)

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Objective: In this project, we are comprehensively studying the function of DJ-1 in PD and GBM to better understand its observed role in both, neurodegeneration and cancer.

Background: Mutations in the PD-associated gene *PARK7* leading to loss of function of DJ-1 protein cause autosomal-recessive PD, whereas high levels of DJ-1 protein were found in different cancer types. DJ-1 is also involved in GBM, a highly aggressive brain tumor that originates from astrocytes and that is associated with increased DJ-1 expression levels. As there is increasing evidence for a metabolic role of DJ-1, the focus is the involvement of DJ-1 in the impaired/increased glucose metabolism in neurodegeneration/cancer.

Methods: To analyze the role of DJ-1 in the regulation of the metabolic switch of increased glycolysis in cancer and impaired metabolism in PD, stable isotope labeled glucose metabolite tracing was used. Metabolomics analysis was performed using human iPSC derived midbrain dopaminergic neurons, human iPSC derived astrocytes of an isogenic trio of wildtype, DJ-1 deficiency and DJ-1 overexpression and GBM cell lines. Astrocytes overexpressing DJ-1 serve as an oncogenic-like model to compare it to the GBM cell lines originating from astrocytes.

Results: In human iPSC derived midbrain dopaminergic neurons of the isogenic trio, glucose tracing showed a significantly increased glycolytic and TCA flux in the DJ-1 overexpression line and a decreased TCA flux in the DJ-1 deficient line. In contrast, glucose tracing in astrocytes of the isogenic trio and a second PD-patient iPSC derived isogenic pair carrying a DJ-1 mutation revealed that overexpression of wildtype DJ-1 increases the glycolytic and TCA flux. In contrast, the loss of DJ-1 significantly reduces the glycolytic and TCA flux in astrocytes. The knockdown of DJ-1 reduces the glycolytic and TCA flux in GBM cells.

Conclusions: Our results show that the effect of DJ-1 on the metabolism in neurons, astrocytes and GBM cells is depending on its different protein levels. High levels of DJ-1 in GBM cells support, and low levels of DJ-1 in PD impair the metabolism. Based on the alterations in the glucose metabolism observed, we aim to identify the molecular target of DJ-1 that is responsible for these metabolic phenotypes in PD and GBM models.

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A secretory vesicle failure in Parkinson's disease occurs in human platelets

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Objective: Since platelets use similar, if not the same, mechanisms to accumulate serotonin (5-HT) as dopaminergic neurons to store DA in their SV; we wonder if a functional failure in the handling of 5-HT would reflect what is happening in dopaminergic neurons and in others of aminergic lineage. This could be diagnostic and prognostic platform.

Background: The presence of high cytosolic concentrations of dopamine (DA) and its metabolites in neurons has been associated with increased vulnerability associated with Parkinson's disease (PD). More than 99% of the amines are confined to secretory vesicles (SV), making these structures crucial for keeping cytosolic DA low. Platelets have been used as cell models of various neurological diseases.

Methods: We have used freshly isolated blood platelets from 70 patients with PD, 113 control individuals and 21 patients with parkinsonism (iatrogenic origin, multi-systemic atrophy, dementia associated with Lewy bodies, progressive supranuclear palsy or parkinsonism of vascular origin). We have carried out a functional assay of 5-HT handling in human platelets in which its basal content and its capacity for accumulation, secretion and spontaneous loss have been quantified.

Results: We found a drastic decrease in 5-HT content and uptake, as well as a decrease in thrombin-induced release in platelets from PD patients, but not in most cases of parkinsonism. Platelets from PD patients had impaired ability to retain 5-HT in SV.

Conclusions: These findings indicate a functional impairment of the SVs for amine handling in patients with PD. We will discuss its use of this technique as i) a biomarker, ii) its potential capacity for preclinical detection of PD and iii) how these tests can serve as a platform to screen disease-modifying drugs.

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A mouse model to test the cortical pathogenic theory of Parkinson's disease

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Objective: To develop a mouse model of chronic corticostriatal overactivity and increase expression of corticostriatal alpha-synuclein.