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Ultra-High Field PET-MRI Imaging for Neurological Disorders – From Parkinson's to Alzheimer's

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Abstract

Increasing demands of in-vivo human brain imaging, both the anatomy and functional molecular imaging brought about development of Ultra-High Field MRI and PET Fusion Imaging (PET-MRI) with 7.0T-MRI and HRRT-PET, a submillimeter resolution PET. With this super-resolution PET - MRI, we have succeeded in visualization of: such as the brainstem Raphe imaging in-vivo human and opened new era in molecular imaging in brain imaging in submillimeter resolution. This talk will discuss possible applications of the system for the early detection of Parkinson's, Alzheimer's, and Strokes, as well as other cognitive science researches such as Phonologic and Logographic language processing in the human brain together with cognitive studies using neural-Lexicons hypothesis for the Cognition and Thinking.

Effects of Health Qigong on Shoulder and Hip Joint Range of Motion, Daily Activities and Motor Function in Patients with Parkinson's Disease

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Abstract

Background and Purpose: Motor dysfunction is a major symptom of Parkinson's disease, which affects daily life. Studies have shown that Taijiquan and Qigong have a good application prospect, both of which can increase the balance function and coordination ability of patients with Parkinson's disease. The purpose of this study was to investigate the effects of Health Qigong on the shoulder and hip joints of patients, as well as the effects on patients' motor ability and daily living.

Methods: Twenty-eight patients with PD were recruited and randomly allocated into either Qigong exercise group or control group with no intervention. The Qigong exercise involved 3-5times each week over 12 weeks. Before and after exercise intervention, daily living and motor function were measured on the shoulder, hip, and Parkinson's comprehensive scales with the Two-way Repeated Measures ANOVA analysis of variance using SPSS version 23.0.

Results and Discussion: Following Health Qigong exercise, Shoulder and Hip Joint Range of Motion was improved by a significant reduction ($P < 0.05$) and daily activities and motor function also had a reduction.

Conclusions: The results show that qigong exercises have a positive effect on joint range of motion and their daily life and motor function. To further explore and provide research direction for guiding the prevention and treatment of Parkinson's disease in the future.

Keywords: Health Qigong, Parkinson's disease, Range of Motion, Motor Function

Yeast Models for Studying Aggregation of Proteins, Involved in Alzheimer's disease

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Abstract

Cross- β fibrous aggregates (amyloids) is implicated in a variety of human diseases. Some amyloids possess transmissible (prion) properties. Amyloid formation by A β and tau proteins has been linked to Alzheimer's disease. Mechanisms of amyloid formation and propagation are still poorly understood due to the complexity of the human organism. Heritable endogenous amyloids, found in yeast cells and termed yeast prions, provide a powerful tool for the investigation of these processes. We have developed yeast assays for studying the prion properties of mammalian and human proteins, and applied these assays to studying proteins associated with Alzheimer's disease (A β and tau). Assays, based on chimeric constructs, containing mammalian or human amyloidogenic proteins (or domains) fused to various fragments of the yeast prion protein Sup35, employ Sup35 as a reporter, enabling phenotypic detection of prion nucleation and propagation. Using such an approach, we have demonstrated transfection of A β amyloids into yeast cells, followed by propagation of various A β -based polymorphs (strains) in the yeast system. We have also studied an impact of A β mutations and some chemicals on amyloidogenic properties of A β . Assays, employing fusions to fluorescent proteins (FPs, specifically GFP, YFP, or CFP), were also applied to characterizing aggregation of A β and tau proteins in yeast. By using this approach, we have demonstrated colocalization of A β and tau aggregates in yeast cells, and addressed the impact of protein kinases on tau aggregation. Our data confirm that the yeast model could provide a valuable information for understanding protein aggregation that is associated with neurodegeneration.

Fungicide Residues Exacerbate β -amyloid Aggregates and Vascular Amyloid Angiopathy in a Mouse model of Alzheimer's disease

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Abstract

Pesticide residues have contaminated our environment and our nutrition over the last century. Although these compounds are present at very low concentrations their long-term effects on human health is of concern. The link between pesticide residues and Alzheimer's disease is not clear and difficult to establish. To date, no in vivo experiments have yet modeled the impact of this chronic contamination on neurodegenerative disorders.

We thus investigated the impact of fungicide residues on the pathological markers of Alzheimer's disease in mouse model. Transgenic (J20, hAPP^{Sw/Ind}) mice were chronically exposed to a cocktail of residues of cyprodinil, mepaniprim and pyrimethanil at 0.1 μ g/L in their drinking water for 9 months. We found that chronic exposure to anilinopyrimidine fungicide exacerbated A β aggregation, microgliosis and neuronal loss. We studied the dynamics of A β aggregation in vivo via a longitudinal study using 2-photon microscopy. Between 6 and 9 months of fungicide residues exposure, we found a substantial increase of vascular amyloid aggregates, reminiscent of cerebral amyloid angiopathy. The mechanism of action involved an over-expression of the levels of the β -secretase cleaving enzyme (BACE1) combined with impairing A β clearance through neprylisin (NEP).

Chronic exposure of the J20 mouse model of Alzheimer's disease to fungicides, at the regulatory concentration allowed in tap water (0.1 μ g/L), strengthened the preexisting pathological markers: neuroinflammation, β -amyloid aggregation and APP β -processing. We hypothesize that prevention strategies towards pesticide long-term exposure may be an alternative to counterbalance the lack of treatment and to slow-down the worldwide Alzheimer's epidemic.

Targeted Metabolomics - Understanding the role of the micro biome in Neurological Diseases

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Abstract

In recent years, a growing number of reports have demonstrated the role of the gut micro biome in the regulation of host brain and central nervous system (CNS) functionality. Surmounting evidence has further supported this notion by revealing connection between gut microbial dysbiosis and pathophysiologies governing neurodegeneration in several CNS disorders.

While it is well-known that gut microbial activity results in the production of metabolites that modulate host physiology, recent work has shown that microbial metabolites can even affect brain function. Importantly, metabolic alterations stemming from microbial dysbiosis have been identified as the missing link by which microbes influence host neurological function.

As targeted metabolomics enables quantitation of metabolites derived from both host and micro biome, this technique enables researchers to identify disease causality long before the manifestation of clinical pathologies.

Here, we present select case studies in which biocrates targeted metabolomics technology enabled meaningful advances in the study of Alzheimer's and Parkinson's diseases. We demonstrate that this approach enabled, not only a better understanding of disease pathogenesis, but also the discovery of predictive biomarkers and new potential therapeutic targets.

Homocysteine and Dementia in Parkinson disease

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Abstract

Parkinson disease (PD) and dementia are neurodegenerative disorders that are frequently seen in the elderly. Homocysteine (Hcy) is an intermediary metabolite from methylation, which is highly relevant to body physiologic activities including DNA metabolism. Elevated plasma level of homocysteine (eHcy) is seen in normal aging and in individuals with neurologic disorders such as PD or dementia. Although clinical observations have confirmed the finding that eHcy is prevalent in PD patients, the former is not a recognized etiology causing PD but rather, an adverse outcome related to the therapy of dopaminergic supplementation. Notably, eHcy may exacerbate various medical and neurologic conditions such as cardiovascular diseases, stroke, mild cognitive impairment (MCI), all of which are potential risks for dementia. The concerns of eHcy relative to dementia in PD (PDD) will be discussed.

Keyword: Dementia, Homocysteine, Neurodegeneration, Parkinson disease

Recent Advances in Understanding Mammalian Prion Structure

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Abstract

Prions are lethal pathogens, which cause fatal neurodegenerative diseases in mammals. They are unique infectious agents and are composed of self-propagating multi-chain assemblies of misfolded host-encoded prion protein (PrP). Understanding prion structure is fundamental to understanding prion disease pathogenesis however to date, the high-resolution structure of authentic *ex vivo* infectious prions remains unknown. Advances in determining prion structure have been severely impeded by the difficulty in recovering relatively homogeneous prion particles from infected brain and definitively associating infectivity

with the PrP assembly state. Recently, however, images of highly infectious *ex vivo* PrP rods that produce prion-strain specific disease phenotypes in mice have been obtained using cryo-electron microscopy and atomic force microscopy. These images have provided the most detailed description of *ex vivo* mammalian prions reported to date and have established that prions isolated from multiple strains have a common hierarchical structure. Misfolded PrP is assembled into 20 nm wide rods containing two fibers, each with double helical repeating substructure, separated by a characteristic central gap 8-10 nm in width. Irregularly structured material with adhesive properties distinct to that of the fibers is present within the central gap of the rod. Prions are clearly distinguishable from non-infectious recombinant PrP fibrils generated *in vitro* and from all other propagating protein structures so far described in other neurodegenerative diseases. The basic architecture of mammalian prions appears to be exceptional and fundamental to their lethal pathogenicity.

Retinal Amyloid Imaging in a Cohort of Patients with Mild Cognitive Impairment and Alzheimer's disease

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Abstract

Accumulating evidence reveals a multitude of pathological changes in the retina of mild cognitively impaired (MCI) and Alzheimer's disease (AD) patients. The retina is the only CNS tissue accessible for noninvasive, patient-friendly, high spatial-resolution imaging including retinal amyloid plaque imaging. Here, using the specific amyloid-binding fluorophore curcumin and laser ophthalmoscopy, we conducted a quantitative and topographical investigation of retinal A β burden in patients with cognitive decline. Thirty-four patients with mostly amnesic MCI were imaged and retinal amyloid count (RAC) and area (RA) were quantified in the supero-temporal quadrant and correlated with demographic and brain volumetric measurements. Total RAC correlated to higher Clinical Dementia Rating (CDR; $r=0.38$, $p=0.02$) and reduced hippocampal volume (HV; $r=-0.39$, $p=0.04$). Retinal subregion analysis revealed significantly higher RAC and RA in the proximal mid-periphery (PMP) in patients with worse dementia, as indicated by Montreal Cognitive Assessment (MOCA) lower than 26 ($p=0.01$; Cohen's $d = 0.83$ and 0.81 , respectively). RAC and RA were increased in the PMP of patients with amnesic MCI and AD compared to cognitively normal patients ($p=0.04$; Cohen's $d = 0.83$). Further, RAC in PAP correlated with reduced HV ($r=-0.41$, $p=0.03$) and higher CDR score ($r=0.37$, $p=0.02$). Altogether, these results suggest that PMP retinal A β count may predict HV and cognitive decline, lending support to retinal amyloid imaging as an accurate and reliable measure of disease progression. Future studies should validate these findings in larger cohorts and evaluate the potential of retinal amyloid imaging in the clinical setting.

ALS Patient Skin Derived iAstrocytes Predicts CuATSM Responsiveness

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Abstract

Patient diversity and unknown disease cause are major challenges for drug development and clinical trial design for Amyotrophic Lateral Sclerosis (ALS). Currently, transgenic animal models do not reflect the heterogeneity of the ALS patient population. Hence, direct translation of potential therapeutics tested in such models to the clinic has proven difficult. To address this, we utilized a rapid reprogramming method to convert skin biopsies from ALS patients into neuronal progenitor cells (NPC) to produce induced astrocytes (iAs). We established a co-culture assay using patient skin derived iAs and mouse

embryonic motor neurons to test potentially therapeutic compounds. We have screened numerous compounds on multiple sporadic (sALS) and familial (fALS) patient lines. Our data indicate a diverse patient response to different therapeutic agents, suggesting shared pathways of interest between patient subgroups. Here we investigated the effects of CuATSM, in clinical trial for ALS, on iAs mediated motor neuron toxicity in both sALS and fALS (mtSOD1 and C9ORF72) lines. We identified CuATSM responders and nonresponders using co-culture assays across patient subpopulations. Next, we performed detailed analysis of the effects of CuATSM on known ALS disease markers. We identified elevated mitochondrial activity in all ALS patient CuATSM responders, which was not present in nonresponders. Treatment of iAs with CuATSM restored this activity to levels comparable to healthy controls. Together these findings suggest that patient iAstrocytes can be sub-grouped based on targetable dysregulated pathways. Importantly, enhanced understanding of cellular profiles could aid in clinical trial design and data interpretation in future studies.

***In-vitro* Modelling and Potential Therapeutic Strategy for NEDAMSS Disease**

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Abstract

The Interferon Regulatory Factor 2 Binding Protein Like (IRF2BPL) is an intronless gene that encodes a member of the IRF2BP family of transcriptional regulators and is ubiquitously expressed. The protein consists of two highly conserved domains, a coiled-coil DNA binding zinc finger domain at the amino terminus and a C3HC4-type RING finger domain at the carboxy-terminus. The gene was initially proposed to play a role in the initiation of puberty in female rodents and non-human primates. More recently, mutations in this gene were associated with NEDAMSS (neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures) disease in children and adults, indicating that the gene might play an important role in both development and neuronal maintenance. Specifically, nonsense variants of the IRF2BPL gene lead to severe neurodevelopmental regression. We have established patient fibroblast cell lines having nonsense variants in the IRF2BPL gene that result in the truncation of its RING finger domain. To study the phenotype in cells from the nervous system, we used an established direct reprogramming method to generate induced neuronal progenitor cells (iNPCs) that can then be further differentiated into astrocytes and neurons. We observed a significant decrease in motor neuron survival in co-culture assays with disease astrocytes as compared to healthy astrocytes. We also established multiple AAV based gene therapy tools to successfully modulate the expression of the protein. Using this in vitro system and the AAV vectors, we are able to study the mechanism of this newly discovered disease and test potential therapeutic strategies.

Mitochondrial and Metabolic Activity Analyses Across Several Neurological and Neurodegenerative disorders Identify Common Therapeutic Targets

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Abstract

There is an urgent need for more effective therapies to treat neurodegenerative and neurological disorders. However, the pipeline for small molecule development and successful implementation into market takes many years. This timeframe is particularly deadly for children suffering from rare neurologic diseases, which are more frequently detected nowadays due to improved sequencing techniques. One approach to accelerate drug discovery is the repurposing of already FDA approved small molecules for the treatment of rare neurological diseases. In order to support the identification of potential therapeutics, knowledge of dysregulated pathways across diseases and individual patients would be beneficial. We developed a rapid reprogramming method for the generation of induced neuronal progenitor cells (iNPCs) that can be differentiated in neurons or astrocytes and used for pathway analysis. We evaluated potential pathways such as ER stress, ROS production, Calcium signaling and mitochondrial metabolism changes in the context of multiple neurological and neurodegenerative diseases. We identified mitochondrial and metabolic activity changes in iAs to be a frequently shared parameter across the disorders. Moreover, treatment of iAs with CuATSM, a drug that is currently in clinical trials for treatment of ALS, successfully restored

mitochondrial activity to healthy control levels across multiple diseases. Together, these findings suggest that small molecule repurposing could be a successful strategy to rapidly develop novel therapeutic approaches to treat rare childhood diseases.

Reversible Cerebral Vasoconstriction Syndrome Secondary to Secreting Jugular Paraganglioma

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Abstract

Introduction: Reversible cerebral vasoconstriction syndrome (SVCR) is a rare entity of variable presentation and etiology, characterized by the presence of thunderclap headache and neurological deficit secondary to multifocal vasospasm. The diagnosis is based on clinical and radiological findings and the management is based on the identification and correction of the etiology to prevent recurrences and fatal outcomes.

Case presentation: A 59-year-old woman with history of resection of a right carotid glomus and imaging finding of left jugular paraganglioma; queries for 15 days of thunderclap headache associated with nausea and emesis without findings of neurological deficit. A brain CT scan showed subarachnoid hemorrhage in the right frontal convexity; a cerebral angiography documented multi-topographic vasospasm with subsequent resolution after intra-arterial administration of nimodipine.

To avoid recurrence, management was established with oral nimodipine; transcranial doppler controls showed resolution of the vasospasm. Given the history of paraganglioma, urine metanephrines test was performed and it was positive. Upon discharge, medical management was prescribed with total resolution of the symptoms.

Conclusions: The identification of etiology is a fundamental part in the diagnostic and therapeutic approach of SVCR. In this case, the tumor is a catecholamine-secreting paraganglioma, so there is a pathophysiological association that is consistent with the evidence and the clinical evolution of the patient.

Inflammation of Organs in Autistic Children

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Abstract

In my previous paper “Diagnosis, prevention, and treatment of Autism via Meridian theory“ 2012, I reported that eight out of 11 autistic children had physiological and behavioral improvement from drinking solution with solid water particles. We have expanded our program to treat more than 100 cases of autistic children and investigated three aspects of inflammation of organs in autistic children. The first aspect is to study the organs with inflammation of an autistic child with great detail. The second aspect it to study the variety of inflammation of the same organ, say the inflammation of the eye of different subjects. Each inflammation is different in shape and severity. The third aspect was that for 28 cases we found (i) 100% autistic children had inflammation of thyroid. (ii) More than 61% autistic children had overactive immune system. (iii) More than 50% autistic children had problems with their large intestine. (iv) More than 21.4% autistic children had problem with their small intestine. (v) More than 46.4% autistic children had problems with their reproductive organs. We conclude that it is important to continue in future that study of many more cases confirms this finding of inflammation of organs in autistic children. In treatment of autistic children, it is necessary to treat other internal organs besides the brain.

Keywords: Autism, Inflammation, Organs, Solid water particles, Brain, Thyroid, Immune system, Large intestine, Small intestine, Reproductive organs

Effects of Health Qigong Exercise on Motor Function in Patients with Parkinson's disease

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Abstract

Background and Purpose: Parkinson's disease is one of the common degenerative diseases of the nervous system, among which motor dysfunction is one of the most common problems that affect the daily life of patients, and seriously affects the mental health and quality of life of patients. This study aimed to determine the effect of Health Qigong as a potential complementary therapy in the obstacle of motor Function in Parkinson Disease (PD).

Methods: Twenty-six patients with PD (aged 67.34 ± 3.70 years) recruited and randomly allocated into either Health Qigong exercise group (n=13) or control group (n=13). Baduanjin is selected for Health Qigong exercise, which is carried out 3-5 times a week for 12 weeks. Before the experiment and after the intervention, a motor function tests (eye-hand coordination test and time up and go test) was performed to evaluate the exercise ability of patients with Parkinson's disease.

Results and Discussion: After exercise intervention, the motor function of patients with Parkinson's disease has been improved. Through the intervention of Health Qigong for 12 weeks, the motor function of patients with Parkinson's disease can be effectively improved (the eye-hand coordination test (left hand: $P < 0.05$; right hand: $P < 0.05$) and time up and go test ($P < 0.05$)), have a positive impact on the quality of life of patients, and achieve the effect of adjuvant treatment.

Conclusions: The present findings suggest that Health Qigong may provide benefits for improving motor function in patients with PD.

Updated Neural Networks in Generalized Epilepsy and Novel Antiepileptic Drugs

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Abstract

We reviewed the alterations of neurotransmitters and neuropeptides in the following brain areas involved in generalized epilepsy: hippocampus, hypothalamus, thalamus and cerebral cortex. In these brain areas, neural networks are also updated. The mechanisms of action of newer antiepileptic drugs, for example a GABAB agonist, an AMPA receptor antagonist and brivaracetam, used in the treatment of generalized epilepsy are also pointed out. Updating the neural networks, we suggest that in the hippocampus GABAergic neurons presynaptically inhibit, via GABAB receptors, epileptogenic neurons. GABAergic, glutamatergic, serotonergic and dopaminergic neurons form the principal neural network, while GABA and serotonin deficiency and dopamine and glutamate hyperactivity have a proconvulsant effect. In preclinical studies, the GABAB receptor agonist GS-39,783 exerted a good antiepileptic effect. Perampanel, an AMPA receptor antagonist, showed good anticonvulsant effects in the treatment of partial-onset seizures and primary generalized tonic-clonic seizures. In this treatment, perampanel can be combined with other antiepileptic drugs. Brivaracetam, the mechanism of action of which will be explained in detail, showed a good efficacy in the treatment of adult focal seizures and secondarily generalized tonic-clonic seizures.

Activation of Autophagy, Inhibition of Inflammation and Amelioration of Behavioural Deficit by Ubisol-Q10 in AD Fibroblasts and Tg(APP^{swe},PSEN1^{dE9}) Mice

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Abstract

Alzheimer's disease (AD) is the most common form of dementia characterized by loss of memory, amyloid-beta plaque buildup and neurofibrillary tangles in brain. Biochemical mechanisms for AD may include oxidative stress, mitochondrial dysfunction, accumulation of damaged proteins/organelles, impaired autophagy/proteasome. Currently, there are no effective treatments to halt the progression of AD, current therapeutics are limited only to symptomatic relief. We have demonstrated that a water-soluble formulation of coenzyme-Q10, Ubisol-Q10, can stabilize the mitochondria, prevent oxidative stress and inhibit premature senescence in fibroblasts from AD patients. Since autophagy plays a critical role in maintenance and survival of neurons, we hypothesized that Ubisol-Q10 treatment could result in resumption of autophagy. Indeed, we observed induction of autophagy by Ubisol-Q10 in AD fibroblasts as well as in the brains of transgenic AD mice. Furthermore, we have reported

unprecedented efficacy of Ubisol-Q10 in protecting neurons in in-vitro and in-vivo models of neurodegenerative diseases. Transgenic animals (AD mice models) fed with this formulation indicated significant improvement in long-term memory and emotional reactivity compared to untreated AD animals. These results were complemented with histochemical analysis that indicated significantly lower amyloid beta plaques and increased autophagy in AD mice. We found increased expression of autophagy related genes beclin-1 and JNK1 following Ubisol-Q10 treatment of AD fibroblasts. These results were confirmed at the protein level by immunofluorescence and Western blotting. Additionally, Ubisol-Q10 supplementation in the drinking water of double transgenic AD mice led to increased expression of beclin-1 and JNK1 in the cortical region. Therefore, the activation of autophagy by Ubisol-Q10, a simple nutraceutical, could halt the progression of AD pathology in transgenic AD.

Targeting Multiple Biochemical Mechanisms with a Novel Nutraceutical Combinatorial Therapy to Halt Neurodegeneration in Parkinson's disease

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Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disease characterized by progressive dopaminergic neuron loss in the substantia nigra (SN) leading to movement coordination impairment. Current therapies such as dopamine replacement and deep brain stimulation only provide symptomatic relief. There are no therapies as of yet that halt the progressive neurodegeneration of PD. Ubisol-Q₄₀, a water-soluble formulation of coenzyme-Q₄₀, and ashwagandha root extract have shown to target different PD pathologies (oxidative stress, mitochondrial dysfunction, autophagy impairment, neuro-inflammation) when used both in-vitro and in-vivo. We evaluated the efficacy of Ubisol-Q₄₀ combined with ashwagandha root extract compared to the agents alone in a paraquat induced rat model of PD. The combined treatment better protected dopaminergic neurons and reduced motor impairments due to paraquat toxicity compared to the agents alone. Compared to the agents alone, the combined treatment better preserved neuron morphology, reduced oxidative stress, enhanced activation of pro-survival astroglia, and inhibited pro-inflammatory microglia, and increased activation of autophagy. Both Ubisol-Q₄₀ and ashwagandha acted as antioxidants but only Ubisol-Q₄₀ resulted in increased autophagy and ashwagandha showed a better anti-inflammatory response. Interestingly, any animals fed ashwagandha that received either paraquat or saline injections showed increased expression of pro-survival brain derived and glial derived neurotrophic factors. Furthermore, the treatments combined or alone showed an increased expression (similar to saline injected control animals) of apoptosis regulator, CARP1 compared to untreated paraquat injected animals. Based on these exciting observations, this treatment composed of two well-tolerated natural products could be developed into a therapy for PD.

Stroke-induced Respiratory Dysfunction and Cognitive Decline: Influence of Sex and Age

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Abstract

Respiratory dysfunction is a common complication of stroke, with an incidence of over 60%. Despite the high prevalence of stroke induced respiratory dysfunction (SIRD) how disordered breathing influences recovery and cognitive outcomes after ischemic stroke is unknown. We hypothesized that stroke induces chronic respiratory dysfunction, breathing instability, and apnea in mice, which would contribute to higher mortality and greater post-stroke cognitive deficits. Mice were subjected to a 60-minute transient middle cerebral artery occlusion (MCAO) or permanent distal MCAO. Whole body plethysmography was performed on C57/B6 young (2-3 month)/aged (20 month) male and female mice. Animals were exposed to a variety of gas conditions to assess the contribution of peripheral and central chemoreceptors. A battery of cognitive tests was performed to examine behavioral function. MCAO led to disordered breathing characterized by hypoventilation and apneas. Progressive cognitive decline correlated with the severity of disordered breathing. Distal permanent MCAO, which produces a smaller

cortical infarct, also produced breathing disorders and cognitive impairment, but only in aged mice. Our data suggests that the incidence of apneas leads to cognitive decline and highlights the influence of aging in breathing disorders after stroke. Therefore, the treatment of respiratory instability may be a viable approach to improve cognitive outcomes after stroke.

The Genes Linking Dementia and Age-Related Comorbidity

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Abstract

We investigated 680 human genes that are associated with co-morbidities (Vahdati Nia et al, 2017; Le et al., 2020). Those genes are involved in lipid metabolism, hemostasis, neuroendocrine and immune functions. Surprisingly, 178 human AD genes (26%) were associated with one or more other neurological diseases, including amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, and schizophrenia. The result implies essential consideration to clinical practice: (1) co-morbidities with Late-Onset Alzheimer's Disease (LOAD) and other neurological conditions; (2) clinical diagnosis of Alzheimer's disease should consider differential diagnosis with other comorbidities. We will discuss age-related comorbidities that link dementia and COVID-19 (Antos et al., submitted). Relevant to this study, we run a special issue to develop our understanding of middle-life processes from normal aging to disease.

The Intervention Study of Health Qigong Exercise on Depression and Anxiety of Parkinson's disease Patients

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Abstract

Background and Purpose: Depression and anxiety are common negative emotions, which will have a negative impact on the life and work of patients. Mild patients will be depressed and depressed. Severe patients may have emotional somatization or even suicidal tendency. The level of anxiety and depression is also an important factor in evaluating people's mental health. Parkinson's disease is a non-communicable chronic disease with no cure at present. With the development of the disease course, patients not only have to endure physical movement dysfunction, but also have a long treatment and economic burden. Combined with the possible pathological changes of the nervous system, patients will be accompanied with depression, anxiety and other mental diseases, which will lead to treatment resistance and prolong the treatment cycle. As the 62nd sport officially recognized by the State General Administration of sports, Health Qigong, as a traditional Chinese health keeping exercise, has the characteristics of gentle and slow movement, moving all over the body, practicing both inside and outside, relaxing and quieting, as well as a variety of individual, collective, music and other practice methods, which can effectively alleviate the negative emotions of the practitioners, It is feasible to improve the mental health of patients with Parkinson's disease.

Methods: This study uses literature method, scale survey method, experimental method, logical analysis method and mathematical statistics method through the Beijing Aerospace Hospital, Yantai City, Shandong Province, Yuhuangding Hospital through the consent of doctors to recruit volunteers, a total of 42 volunteers recruited, volunteers randomly divided into Health Qigong group and control group, during the experiment Health Qigong group 1 subject had Health Qigong practice experience, 2 subjects can not complete the exercise according to the requirements, the control group 1 subject data collection is not complete. One subject participated in other types of sports, one subject was unable to complete the experiment due to low compliance, and was eventually included in the statistical results of the Health Qigong group of 18 people in the control group of 18 people. On the basis of normal medication prescribed by the doctor, the Health Qigong group increased the Health Qigong exercise five times a week for 60 minutes and 12 weeks, and the control group followed regularly to ensure that no specialized physical activity was performed during the experiment. The two groups were given questionnaires before, 6 and 12 weeks after the trial began, using the Hamilton Depression 17 Scale (HAMD17) and the Status- trait (S-TAI) Anxiety Scale.

Results and Discussion: After 12 weeks of experiment, the total score of state trait anxiety scale, Hamilton 17 item depression scale and blocking factor had interaction effect ($P = 0.046$, $P = 0.011$, $P = 0.041$). There were significant differences in the total score of Hamilton 17 item depression scale and blocking factor between the Health Qigong group and the control group ($P = 0.008$, $P = 0.001$); There were significant differences in total score of state trait anxiety scale and cognitive impairment factor

between groups ($P = 0.019$, $P = 0.017$), and significant differences in state anxiety, trait anxiety and cognitive impairment factor among groups ($P = 0.023$, $P = 0.023$, $P = 0.017$); There was no significant difference between the two groups ($P = 0.262$); There was no significant difference in body mass factor and sleep disorder factor between and within groups. There was no significant difference in total score of state trait anxiety scale, state anxiety, trait anxiety, total score of Hamilton 17 item depression scale, cognitive disorder factor, body anxiety factor, blocking factor, body weight factor and sleep disorder factor in the control group.

Conclusions: On the basis of not changing the drug treatment, 12 weeks of Health Qigong exercise can significantly improve the attention, enthusiasm for life, self-identity and depression, and anxiety, which indicates that Health Qigong exercise can alleviate the negative emotions of Parkinson's patients and improve their enthusiasm for life.

Keywords: Health Qigong, Parkinson's disease, anxiety, Depression.

Alzheimer's disease Candidate Biomarkers miR-483-5p and miR-200a-3p Control Tau Phosphorylation and Amyloidogenesis

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Abstract

MicroRNAs are key regulators of gene expression in the physiology and pathology of a range of diseases including Alzheimer's disease (AD). Circulating miRNAs in blood plasma could serve as a non-invasive biomarkers alternative to the currently available diagnostic approaches, such as brain imaging, which requires sophisticated equipment, and cerebrospinal fluid (CSF) analysis, which requires a lumbar puncture. Recently, we described a panel of miRNAs in plasma of early-stage AD patients, of which miR-483-5p and miR-200a-3p were the most significantly upregulated. Using the publicly available tools such as miRTarBase and TargetScan, we identified likely targets of these miRNAs known to be strongly associated with AD pathology: TAU, ERK1 and ERK2 for miR-483-5p and amyloidogenic secretase BACE1 for miR-200a-3p. Employing several cellular methods, we confirmed that hsa-miR-200a-3p regulates BACE1 mRNA. Also, we found that miR-483-5p reduces phospho- and non-phospho- ERK1 and ERK2 at both mRNA and protein levels. This led directly to reduction of TAU phosphorylation at sites consistent with AD-associated TAU aggregation. These results indicate the co-regulation of amyloid and tau pathology by miRNAs in AD. Moreover, the increase in miR-483-5p and miR-200a-3p found in AD plasma may be the result of the physiological response to the incipient AD pathology. As such, the miR-483-5p and miR-200-3p could be viable targets for the development of disease-modifying AD therapies.

Neuropsychological Assessment of Semantic Dementia: Possibilities within Contexts without Sufficient Psychometric Evidence

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Abstract

Semantic dementia is one of the clinical subtypes of the so-called frontotemporal dementia. At the neuropsychological level, it is characterized by a series of problems at the level of different psychological functions, processes, and sub-processes, the most characteristic being alterations at the level of explicit memory systems, especially at the level of semantic sub-components. Possible deficiencies at the level of executive functions, mainly at the level of its verbal components, are not ruled out.

Its neuropsychological assessment can be carried out through the coordinated use of different tests and/or clinical batteries (for example, the Weschler scales), focused on exploring the problems present in the case in a global way as particular. However, in countries where there is not enough psychometric evidence, it is possible to make a qualitative adaptation of these instruments to the reality of each patient, focusing their clinical analysis at the level of the different types of response, thus generating useful evidence for defining both the diagnosis and the future intervention plan to be introduced.

Keywords: Semantic insanity, frontotemporal dementia, amnesia, working memory, executive functions, neuropsychological assessment.

Ubisol-Q10 Induced Autophagy Resumption Ameliorates AD Pathologies in Presenilin-1 Mutated Fibroblasts and Transgenic AD Mice

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Abstract

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder worldwide, affecting approximately 35 million individuals according to the World Health Organization. Common symptoms include memory loss, the formation of amyloid-beta plaques, and neurofibrillary tangles. These features could be directly related to neuronal cell death occurring in both the cerebral cortex and hippocampal regions of the brain. Pathologies associated with AD are often credited to four main biochemical mechanisms including dysfunctional mitochondria, elevated levels of oxidative stress, neuroinflammation, and autophagy deficiencies. However, rather than targeting these biochemical pathways to inhibit the progression of AD, current treatments tend to focus solely on symptomatic relief. Prior in-vitro experimentation has demonstrated the ability of a water-soluble formulation of coenzyme-Q10, Ubisol-Q10, to stabilize mitochondria, reduce oxidative stress, and prevent the onset of stress induced premature senescence in fibroblasts obtained from AD patients (PSAF). We hypothesized that Ubisol-Q10 could induce autophagy, which is crucial for the maintenance and survival of neurons. Indeed, this result was observed in PSAF and the brains of transgenic AD mice whereby autophagy induction occurred following Ubisol-Q10 supplementation. Increased expression of autophagy associated genes including Beclin-1 and JNK1 was observed at both the mRNA and protein levels through qRT-PCR, immunohistochemistry, and Western blotting. Furthermore, transgenic AD mice exhibited reduced amyloid-beta plaque formation with both long-term and spatial memory improvements following Ubisol-Q10 supplementation. These results suggest that autophagy plays a crucial role in neuronal health and Ubisol-Q10 treatment may help to inhibit the progression of Alzheimer's disease.

Morphological Analysis of New Cytopathological Hallmarks in Dopaminergic Enteric Neurons of Parkinson's disease

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Abstract

Parkinson's disease (PD) is the second most frequent neurodegenerative disease in the world. The main histological hallmark is the accumulation of misfolded α -synuclein, conforming Lewy bodies and Lewy neurites and loss of dopaminergic neurons in substantia nigra pars compacta (SNpc). There have been described alterations in Golgi apparatus (GA) organization, which is the central organelle of intracellular traffic, in PD and other neurodegenerative diseases. Our previous studies, using cellular models of PD, demonstrate that GA fragmentation is an early event previous to α -synuclein aggregation and cytoskeletal alterations (1) and recently we have found that the SNARE protein syntaxin 5 forms extracellular aggregates resembling the amyloid plaques characteristic of Alzheimer's disease in dopaminergic neurons in human samples of SNpc of PD patients (2).

Moreover, there is also evidence of this pathology not only in the central nervous system, but also in the enteric nervous system (ENS) neurons, which has drawn attention in the last years. Recently, gastrointestinal symptomatology, previous to motor symptoms in PD, has been the reason to think that lesions in ENS could develop earlier in the course of the disease, therefore, the study of ENS could help to understand this pathology. The purpose of this study was to analyze, using morphological techniques, the structure of GA, and cytoskeleton organization of enteric dopaminergic neurons of an experimental hemiparkinsonian rat model induced by 6-OHDA. The results obtained showed alterations in GA cytoarchitecture, cytoskeleton microtubules organization and Syntaxin-5 (SNARE). These findings support the ENS as object of study of possible specific biomarkers for early diagnosis of PD.

WHO Grade III Anaplastic Astrocytoma in A 72 Years Old Male-A Case Report

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Abstract

Glioma is a common type of tumor that originates in the glial cell in brain and is devastating in nature. It can affect all age groups but is more common in adults and has been found more in males than in females with a ratio of 1.3/1. Despite the aggressive treatment it relapsed and can cause mortality because of its infiltrative nature. This WHO type III Anaplastic Astrocytoma is more common in 40-50 years old with a median of 41 years.

Here, we report a new case of Glioma occurring in a 72 year old male, who presented with a right sided headache, forgetful, worsening memory, behavioral problem along with increased agitation and irritability. MRI Brain WO/W revealed a mass in the left thalamus and basal ganglia region with a thick rim of peripheral enhancement. Diagnosis of Anaplastic Astrocytoma (WHO Grade III) was confirmed by histology and immunohistochemical analysis of the tumor. It is a case of Left sided WHO GRADE III Anaplastic astrocytoma which is rare in this age group of 72 years. The patient was managed with gamma knife radiosurgery, chemotherapy with Temozolomide (TMZ), and targeted molecular therapy with Bevacizumab. The patient improved with remission of symptoms.

The Melting Pot of Moyamoya Disease: Lessons from a Challenging Case

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Abstract

Objective: To illustrate a case of delayed diagnosis of Moyamoya disease after the patient didn't identify with the conventional phenotype, resulting in delayed diagnosis.

Background: Moyamoya disease (MMD) is a rare, idiopathic vasculopathy of the intracranial ICA and its proximal branches. In the setting of chronic ischemia, small collateral vessels proliferate at the base of the brain, their appearance likened to a "moyamoya" (puff of smoke) by early Japanese investigators. Patients may present with a broad spectrum of neurological symptoms arising from global cerebral hypoperfusion, focal infarcts, and the hemorrhage of fragile collaterals. Although the 'illness script' of MMD conventionally involves young Asian patient without vascular risk factors, demographic studies have found that a moyamoya patient in the United States is actually more likely to identify as Black than to identify as Asian.

Design/Methods: A 36-year-old African-American man with hypertension, DM2, and MMD presented for neurological follow-up after undergoing STA-MCA bypass. Prior to his diagnosis with MMD, the patient suffered two cerebrovascular accidents complicated by residual right-sided hemiparesis and hypoesthesia, dysarthria, and impaired concentration. His first stroke occurred at age 31 attributed at the time to cocaine-induced vasospasm, despite the patient adamantly denying illicit drug use. An MRI was not performed, and he was released without close neurological follow-up. At the age of 35, he experienced a second stroke with worsening of right-sided deficits and was referred to a higher level of care. MRA demonstrated severe narrowing of the left supraclinoid ICA with a paucity of signal in the A1/M1 branches and a paucity of signal in the A1/A2 branches of the right ICA. Slight collateralization was appreciated bilaterally. Based on characteristic MRA findings, the diagnosis of MMD was established. The patient was prescribed aspirin and subsequently underwent STA-MCA bypass. His surgical recovery was uneventful. However, he presented to our office 3 months postoperatively because of continued headaches, weakness, and difficulty concentrating. He was also concerned about a hereditary component to his illness and requested genetic testing.

Results: Neurological examination demonstrated deficits stable from the patient's second stroke. He was prescribed analgesia for headaches and counselled that existing deficits were unlikely to improve after surgery. Genetic testing performed through 23andMe revealed 11.8% Japanese ancestry, suggesting an occult genetic predisposition to moyamoya disease.

Conclusions: Moyamoya disease is a challenging clinical entity, and delay in treatment can lead to extensive neurological morbidity and mortality. The initial medical team's premature closure on cocaine-induced vasospasm—and failure to investigate alternative causes of stroke such as MMD—likely relates to the fact that our patient presented as Black rather than as Asian. The case is a stark reminder that conditions once identified with a single ethnic phenotype now occur across multiple phenotypes, and that it is important for clinicians to actively unlearn limiting associations that delay diagnosis

Design/Methods: A 36-year-old African-American man with hypertension, DM2, and MMD presented for neurological

follow-up after undergoing STA-MCA bypass. Prior to his diagnosis with MMD, the patient suffered two cerebrovascular accidents, the first occurring at age 31 and second at age 35. After the second stroke, MRA demonstrated severe narrowing of the left supraclinoid ICA with a paucity of signal in the A1/M1 branches and in the A1/A2 branches of the right ICA. Based on characteristic MRA findings, the diagnosis of MMD was established. The patient presented to our office 3 months postoperatively because of continued symptoms and requested genetic testing.

Perseveration and Anterograde Amnesia: The Broken Record Phenomenon

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Abstract

Transient global amnesia (TGA) is a clinical syndrome described as sudden onset of temporary anterograde amnesia, along with mild retrograde amnesia, that resolves within 24 hours. A 67-year-old Caucasian female with a history of microvascular compression syndrome with associated vertigo s/p multiple cranial nerve decompression surgeries presented with altered mental status. Upon presentation, she repeated the same story every two minutes, was unable to recall events prior to admission, and was A&Ox1. She denied any pertinent history. CBC, CMP, ESR, PT/INR, B12, folate, homocysteine, drug and alcohol screen, and urine dipstick were within normal limits. EEG, CT and MRI of brain, and EKG were negative for acute findings. After 24 hours without treatment, she was without perseveration and A&Ox4. After ruling out other more common conditions, the diagnosis of exclusion TGA was made. TGA, otherwise termed the “broken record” phenomenon, remains a rare syndrome with largely unknown etiology. It is most common in patients greater than 50 years old and has an incidence estimated to be 5.2-10/100,000. Patients present with disorientation, anterograde amnesia, and perseveration which can include repetitive questioning; however, they do not lose self-awareness or exhibit focal neurological deficits. Clinical diligence is necessary to rule out acute differentials, including stroke, seizure, acute delirium, metabolic encephalopathy and drug intoxication. Working through these less probable differential diagnoses allows for TGA, a diagnosis of exclusion, to be established. Due to rarity of this syndrome, clinicians require awareness of the presentation of TGA for appropriate utilization of hospital resources and patient care.

Characterization and Correlation of Neurodegeneration and Biological Markers of Model Mice with Traumatic Brain Injury and Alzheimer’s disease

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Abstract

Alzheimer’s disease (AD) is a predominant type of dementia and major cause of neural network impairment. There are currently no known cures for the disease. Early detection to impede its progress is the current standard. Beyond age and genetics, another prevalent risk factor for AD might be traumatic brain injury (TBI), which has similar neurodegenerative hallmarks. Our research focuses on obtaining information and methods to be able to predict when neurodegenerative effects might occur at a clinical level by observation of events at a cellular and molecular level in mice. We introduce our evidence that brain damage can be observed via brain imaging prior to noticeable loss of neuromuscular control in AD model mice. We then show our evidence that some blood biomarkers might be able to be early predictors of AD in the mice. Here we search early predictors of long-term neurodegenerative effects due to differing degrees of TBI and AD, and what level of TBI causes further damage and earlier death to the AD mice. Upon application of TBIs to induce extremely mild TBIs, wild-type (WT) mice and AD mouse models were tested for epileptic activity, neuromuscular control, olfactory ability, blood biomarkers, and brain imaging. Our data suggests that neuromotor control and olfactory function diminish for both AD and WT mice after the administration of multiple consecutive, mild TBIs. Greater enhancement of AD symptoms is observable in older mice compared to younger mice following TBI. Sustained TBI causes both accelerated and exacerbated AD symptoms in AD model mice.

Influence of Novel Corona Virus Disease (COVID.19) on Parkinson’s disease: A Systemic Review

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Abstract

Background: SARS-COV2 binds to the host angiotensin-converting enzyme 2 (ACE2) receptors. Cells expressing ACE2, act as entry portals for SARS-CoV-2 infection and invade the central nervous system (CNS). Parkinson's disease (PD) has been seen after some post-viral infections.

Methods: We conducted a database search on PubMed, Science Direct, Google scholar and Embase databases using the keywords "COVID-19", "Parkinson's disease", "SARS-COV-2," "Pandemic", "Neuromuscular conditions". Studies included all those involving PD patients with COVID-19 infection while non-COVID and pregnant patients were excluded.

Results: All together describing a total of 1290 Parkinson's patients with COVID-19. Male gender was predominant in 10 studies out of 16 and Average mean age was 76.9 and average disease duration was 11 years. Almost most of the patients reported to have other comorbidities, most common were hypertension, Diabetes, Obesity, Dyslipidemia, Cardiovascular disease, immunocompromised, COPD, asthma and chronic renal and liver diseases. Of the Parkinson's patients that were tested and positive for infection with SARS-CoV-2, worsening of motor symptoms including bradykinesia, Tremors, gait disturbances, Delirium and Dementia and severe spasms of arms and legs reported, with individual study percentage ranging from 19% to 100%, along with other COVID-19 symptoms. Encephalopathy was also one of the main symptoms presented in 2 of the studies. Mortality rates for those who were hospitalized ranged from 5.7% to 100%.

Conclusion: PD patients may experience substantial worsening of motor and nonmotor symptoms during COVID 19 infections.

Application of Artificial Intelligence in the Prevention, Diagnosis and Treatment of Alzheimer's disease: New Hope for Dealing with Ageing in China

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Abstract

Alzheimer's disease (AD) has become a major issue around world. AD is the sixth leading cause of death across all ages and the fifth leading cause of death for those aged ≥ 65 years in the United States. In China, the overall prevalence of AD was calculated to be 0.04(95% CI:0.04-0.05), and increased significantly from 404 per 100,000 people in 2007 to 624 per 10,000 people in 2014. In addition, the incidence and prevalence of AD is increasing with age. Recent statistics showed that, by the end of 2017, elderly population was nearly 240 million, with the largest elderly population in the world. So, the health expenditures and costs of care for AD patient is very heavy in China. Currently, the two major challenges for AD are the difficulty in early detection and poor treatment outcomes. Fortunately, progress in genomics, proteomics and medical imaging, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) and so on, holds promise for earlier diagnosis of AD and identifying candidate therapeutic targets. However, processing such different kinds of massive data is very time consuming for doctors and researchers. Increasing evidence showed that artificial intelligence (AI) technologies, including deep learning systems, are one potential solution for analyzing various kinds of data automatically to make diagnosis and find new drugs. However, it is still in its infancy. More researches should be conducted to improve the prognosis of patients with AD in the future.

METTL3 Facilitates Arc Expression via YTHDF1-mediated m6A Modification

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Abstract

Activity-regulated cytoskeleton-associated protein (ARC), a member of immediate early genes (IEGs), can be activated after the induction of long-term potentiation and plays important roles in the synaptic plasticity to consolidate memory. Studies have shown that the abnormal expression of ARC in the brains of Alzheimer's disease (AD) patients can lead to the disturbance of synaptic plasticity, which is closely related to the occurrence of AD. The ARC expression is mainly regulated by the complex and flexible epigenetic modification. However, as the most common epigenetic modification of eukaryotic mRNA, whether N6-methyladenosine (m⁶A) engages in the modification of ARC remains unclear. Here, we investigate the role of m⁶A modification in the regulation of ARC expression in AD. The ARC expression was apparently reduced in AD patients and cellular models. There were 5 m⁶A modification sites of ARC mRNA predicted by SRAMP database, and ARC was confirmed as the target gene of methyltransferase-like 3 (METTL3) by MeRIP. Beta-protein amyloid (A β) decreased the m⁶A modification, accompanied by METTL3 and YTHDF1 homology domain family protein member 1 (YTHDF1). Knockdown of METTL3 substantially decreased ARC mRNA m⁶A modification and declined ARC expression. While METTL3 overexpression retrieved the ARC expression after A β treatment. The ARC expression decreased after knockdown of YTHDF1, and overexpression of YTHDF1 could not rescue the loss of ARC expression after 3-deazaadenosine treatment or knockdown of METTL3. In conclusion, our findings identify that METTL3 induces the ARC expression via YTHDF1-mediated m⁶A modification, which suggests an important mechanism of epigenetic alteration in AD.

Prenatal Exposure to Low Doses of Fungicides Corrupts Neurogenesis in Neonates

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Abstract

Neurogenesis plays a crucial role during neurodevelopment and its dysfunction can lead to neurodevelopmental disorders. A recent hypothesis stipulates that exogenous factors could corrupt this process and predispose to neuropathological disorders later in life. The presence of pesticide residues in the diet represents a threat of which we have recently become aware of. Indeed, they could corrupt neurogenesis, especially during gestation, potentially leading to impaired neuronal and synaptic functions. We investigated the impact of fungicide residues on WT mice exposed throughout gestation. Thus, mice were exposed to fungicides, cyprodinil, mepanipyrim and pyrimethanil, alone or in cocktail. Exposure was performed through drinking water at the regulatory limit dose of the European countries (0.1 μ g/L). Results showed that gestational exposure to fungicide residues substantially promoted an increase of neural precursor cells at P3. This corrupted neurogenesis was linked to increased levels of β -catenin, likely through the crosstalk of the PI3K/Akt and Wnt/ β -catenin pathways, both involved in cell proliferation. Fungicide exposure also altered protein expression of PSD95 and NMDA /AMPA receptors in P3 neonates, two targets of the β -catenin signaling pathway. Adult neural stem cell extractions from mice treated with the fungicide cocktail, showed an increase proliferation and differentiation combined with a reduction of their migration properties. To conclude, corruption of neurogenesis by this chemical assault could be a fertile ground for the development of neurological diseases later in life.

Assessing Ketorolac Analgesic Effect in Postoperative Pectus Excavatum and Pectus Carinatum Patients: An Observational Study

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Abstract

An objective measurement of pain and analgesic efficacy is currently an unmet need. The current Visual Analog Scale does not consider the etiology of pain or directly guide specific intervention to treat the processes underlying pain transmission. This observational pre/post study utilized a novel method employing pupillary reflex dilation to evaluate the analgesic effect of Toradol. Measurements were taken in postoperative pectus excavatum and pectus carinatum patients at Children's National Medical Center who received Toradol as part of their standard care. Pupillary reflex dilation to a stimulus was measured at baseline prior to administering Toradol and one hour following administration. The dilation was elicited via an electrical stimulus at 2000, 250, and 5 Hz for the A β , A δ , and C-fibers, respectively, with an intensity based on the baseline perception

threshold. Paired t-tests were used to compare amplitudes and areas under the curve for each fiber type pupillary dilation curve, pre- and post-Toradol. There was no statistically significant change in amplitude following Toradol administration for any fiber type. Toradol had statistically significant effects on the AUC of the C-fiber ($p < 0.05$), effects trending toward significance on the AUC of the A δ fiber, and no statistically significant effects on the AUC of the A β . This study supports the use of the tested technology towards in determining the impact of an analgesic on nociceptive pain. Future study into analgesic drug effect should utilize this method to objectively classify the type and intensity of a patient's pain, and the fiber-specific effect of the analgesic prescribed.

Von Recklinghausen Disease – Seizures and Gliomas – A Case Report

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Abstract

Background: Von Recklinghausen disease (Neurofibromatosis type 1, NF1) refers to an autosomal dominant genetic disorder that is characterized by the development of multiple benign (non-cancerous) tumors that impact the nervous system and skin (neurofibromas). This disorder has a prevalence of one in 3,000 births and a high frequency of mutation leading to variable presentations ranging from benign lesions to nonfunctional impairment with complications. Such complications vary based on age and can include psychiatric disorders (anxiety, dysthymia, depression), chronic low back pain with scoliosis, and even seizures. NF1 has a higher seizure prevalence compared to the general population; however, the rationale behind this is difficult to elucidate due to when and how seizures are diagnosed as well as if provoking factors are present.

Case: We present a case report of a 20-year-old male with a documented history of NF1, since the age of three, who presented to a local hospital for evaluation of an unwitnessed seizure with loss of consciousness/bladder control. He underwent an MRI without contrast which demonstrated hyperintensities bilaterally over the mesial temporal lobe along with a FLAIR hyperintensity lesion near the splenium of the corpus callosum. He later became combative and experienced another seizure event requiring intubation. A repeat MRI with contrast demonstrated a faint enhancement of the splenial lesion. He later underwent EEG monitoring which was unremarkable.

Conclusion: We present a case with a tumor of the splenium of the corpus callosum and NF1. The imaging characteristics provide a possible rationale for a higher seizure frequency in NF1 patients compared to the general population.

Features of Cytokine Changes and Food Reactions in Children with Autism

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Abstract

Children with ASD are 2 times more likely to have IgG-dependent sensitization to food antigens (fAg) of dairy and grain products relative to the comparison group. In this case, the values of the total titers of specific IgG to fAg significantly correlate with the number of points obtained during testing in the ATEC questionnaire. It was revealed that the diagnosed yeast sensitization to *C. albicans* negatively affects not only specific hyperreactivity, but also the number of fAg, which is directly correlated with serum IFN γ concentrations.

Correlation was established between the amount of fAg, the spectrum of IgG-food hypersensitivity and increased serum concentrations of IFN γ , IL6, IL17 cytokines against the background of lower IL4 concentrations. A deficiency of vitamin D3 (25 (OH) D) has been established, despite the constant intake of preventive doses of vitamin. Indicators of IL-17, IL6, IFN γ are inversely correlated with vitamin D3 deficiency.

Following the recommended personalized elimination diet for 6 months by children leads to a significant decrease in the concentration of IgG to antigens of dairy products, which coincides with a decrease in the score of the ATEC test.

The results of this study are of theoretical and practical interest, since they supplement the existing ideas about the relationship of specific food hypersensitivity with the processes of initiation and maintenance of immune inflammation, with the psychophysiological status in children with ASD.

The Added Value of Delayed T1 Post Contrast Sequence in Diagnosis of Multiple Sclerosis

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Abstract

Aim of the work: The aim of this study was to assess the rule of delayed T1 post contrast sequence in detection of active lesions in multiple sclerosis patients by comparing the early and delayed T1 post contrast images.

Materials: This was a prospective study and included 30 known multiple sclerosis patients with clinically suspected activity referred from neurology department to radiology department for MRI examination.

Methods: All patients were subjected to the followings: 1- Conventional routine MRI of the brain using 1.5 T machine. 2- T1 delayed post contrast sequence (about 10 min after contrast injection).

Results: The included MS cases showed 162 lesions of variable distribution as 113 lesions were supratentorial while 49 lesions were infratentorial. Among 162 lesions in the current cases 58 lesions showed post contrast enhancement while the remaining 104 lesions were non enhancing. From the total of enhancing lesions (58), 16 lesions showed early enhancement while 42 lesions showed delayed enhancement.

Conclusion: Delayed T1 post contrast is an important sequence for detection of active MS plaques as it increases the sensitivity of MRI.

Chromosomal Sex Differences in Tau Levels in Patients Attending a Memory Clinic

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Abstract

Background: Abnormal tau proteins can destabilize microtubules and cause an aggregation of hyperphosphorylated tau in neurodegenerative diseases like Alzheimer's Disease (Medeiros, 2011). Two thirds of people diagnosed with dementia are women (Mielke, 2018). Understanding how sex can affect one's tau protein levels in the context of memory loss is important. The effect of female chromosomal sex on tau proteins is currently unknown.

Objectives: To analyze CSF tau protein variation among male and female patients attending a memory clinic.

Methods: Memory clinic patients from July 2010 to July 2019 with available CSF tau results were analyzed retrospectively. Univariate and multivariate analyses of tau with sex, age, race, and education were performed.

Results: From July 2010 to July 2019, 100 patients had recorded tau protein levels - mean (401.12 ± 278.15), age at first visit (71.00 ± 13.79). 56.87% of the sample were females and 88.83% were Caucasians. Univariate analyses of tau levels (Rho = -0.09 p = 0.39), race (Rho = -0.18 p = 0.07), and age after adjusting for sex, education, and race (Rho = P= 0.0001*) indicated no sex variability. A multivariate model did not show sex variability.

Conclusions: Sex variation in tau protein is not present in the memory clinic patients.

The Modulation of Expanded GGCCTG Repeats Toxicity by Surrounding Sequences in Fly Models of SCA36

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Abstract

Spinocerebellar ataxia 36 (SCA36) is a neurodegenerative disorder that is caused by a GGCCTG hexanucleotide repeat expansion in the first intron of *NOP56* gene. How such repeat expansion causes SCA36 is largely unknown. To examine the potential pathogenic mechanisms that lead to SCA36, we assembled 100 pure GGCCTG repeats from a short synthetic GGCCTG repeat sequence, and generated transgenic fly lines with the 100 pure repeats embedded with different sequence contexts and with different reporter tags to model human SCA36. Transgenic flies carrying the expanded repeats were crossed with specific drivers for tissue specific expression. When the pure repeats were expressed in the eyes, they caused rough eye phenotype in select lines, a characteristic phenomenon in fly models of neurodegenerative diseases. The severity of the rough eye phenotype were associated with shorter 3' expression tags and also seemed to be dependent on the expression level. Our results suggest that the GGCCTG hexanucleotide repeats toxicity is dependent on the specific contexts, which can partially explain why *NOP56* to be the host gene of these expanded repeats for the disease.

C11, A Novel 2-(2,5-dioxopyrrolidin-1-yl) Propanamide Derivative as a Candidate for a Broad-spectrum Antiepileptic Drug: Its Impact on Neurogenesis, Neurodegeneration and Cognitive Functions in Mice

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Abstract

Looking for a new potent anticonvulsant we synthesized a hybrid compound derived from 2-(2,5-dioxopyrrolidin-1-yl) propanamide (C11). The compound C11 as a hybrid molecule merges on common chemical template the structural fragments of clinically relevant antiepileptic drugs (AEDs) such as ethosuximide ETS, levetiracetam LEV, and lacosamide LCM.

The aim of the presented study was *in vivo* evaluation of the neurogenesis and neuronal damage processes, as well as cognitive functions in mice treated with a new potent anticonvulsant C11 in comparison to the efficacy of AEDs. All experiments were performed on adolescent male C57/BL mice. The following drugs were used: C11 (20 mg/kg), LEV, LCM, ETS (10 mg/kg). Confocal microscopy and cell counting was done using Zeiss microscope and ImageJ software.

C11 as well as LEV and ETS did not disturb the proliferation of newborn cells compared to the control mice, whereas LCM treatment significantly decreased it. Chronic AEDs therapy did not induce significant neurodegenerative changes. Behavioral studies with using Morris Water Maze test did not indicate any disturbances in the spatial learning and memory after C11 as well as LEV and ETS treatment in comparison to the control group except LCM mice, where significant dysfunctions in time, distance and direct swim to the platform were observed. Interestingly, results obtained from *in vivo*.

A new hybrid compound C11 in contrast to LCM has no negative impact on the process of neurogenesis and neurodegeneration in the mouse hippocampus. Furthermore, chronic treatment with C11 turned out to have no negative impact on cognitive functions of treated mice, which, is certainly of great importance for further more advanced preclinical and especially clinical trials.

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Evaluating the Link between Alzheimer Associated-APOE Variants and Lyme Disease

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Abstract

The apolipoprotein E4 (APOE4) variant is considered to manifest the highest genetic risk factor for Alzheimer's disease (AD) compared to other variants. It exhibits an increased synapse number and elevated Amyloid-Beta (A β) secretion and Tau protein aggregates compared with isogenic APOE3 cells. Further studies comparing different cell lines such as BE2C expressing APOE3 and Kelly expressing APOE4 can contribute to understanding the influence of the variants on AD. To assess the sensitivity of these cell lines, they will be subjected to the oxidative-stress effect of Menadione DNA-damaging agent. The cell viability will be analyzed by using almar-Blue assay. Also, flow cytometry would be performed for quantitative analysis of superoxide reactive oxygen species. Furthermore, to evaluate how Lyme-causing bacteria can contribute to the development and/or progress of AD. Both of these cell lines will be infected by *Borrelia burgdorferi*. The level of Amyloid precursor protein and the rate of amyloid beta plaques formation will be assessed respectively. Results of this study can help us understand the correlation of the downstream effect of chronic infection along with oxidative stress, and the presence of APOE4 variant and if they would accelerate the development and or progress of AD.

Concussion severity in pediatric mTBI from organized vs non-organized sports as measured by serum GFAP and UCH-L1

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Abstract

Background: This prospective cohort study evaluated whether there were concentration differences in biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1) in the serum of children in three injury groups; concussion from: 1) trauma unrelated to sports, 2) organized sports, and 3) non-organized recreational activities. This study also examined the performance of biomarkers in predicting intracranial lesions on CT scan.

Methods: This cohort study enrolled a convenience sample of children presenting to three Level 1 Trauma Centers following blunt head trauma with a GCS 15 and having been diagnosed with concussion based on the American Congress of Rehabilitation definition. Single blood samples of 2.5-5 ml (based on weight) were obtained within six hours of injury and measured by ELISA for GFAP and UCH-L1 (ng/ml).

Results: A total of 131 children with concussion were enrolled. Median GFAP levels were 0.16 (IQR 0.05-0.48) in no sports, 0.07 (0.008-0.26) in sports, and 0.41 (0.08-0.84) in recreational (p=0.013). Median UCH-L1 levels were 0.18 (IQR 0.10-0.31), 0.28 (0.13-0.49), and 0.32 (0.20-0.63) respectively (p=0.002). GFAP was significantly higher in recreational versus sports (p=0.008). UCH-L1 was significantly higher in recreational versus no sports (p=0.001). The respective AUCs in each group for CT+ for GFAP were 0.93 (0.86-1.00), 0.95 (0.84-1.00), and 0.77 (0.55-0.98) and for UCH-L1 were 0.88 (0.76-1.00), 0.65 (0.27-1.00), and 0.79 (0.54-1.00).

Conclusion: Serum concentrations of GFAP and UCH-L1 were highest in group 3, which also demonstrated the highest CT+. Non-organized recreational activities can thus lead to significant brain injury.

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