ECN2021

In association with The Oxford Centre for Neuroinflammation

ECN2021

The Virtual 2nd European Conference on Neuroinflammation

Basic and Clinical Concepts

12-13 April 2021

Abstracts Book

A Pilot Study of Attitude and Perception of Multiple Sclerosis Patients Toward Exercise

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Introduction

The aim of this pilot study was to compare the attitude of Multiple Sclerosis patients from Britain and Kuwait toward exercise

Methodology

A questionnaire was distributed to 200 individuals with MS (100 Kuwaiti, and 100 British). The questionnaire consists of three parts; 1. General demographics, 2. Disease specific data (symptoms, severity levels, relapse frequency, and support system), and 3. Attitudes towards physical exercise.

Results

A response rates of 62% from the British sample, and 50% from the Kuwaiti sample was achieved. 84% of the sample (n=52) were 41 years old or over. The duration of the disease was less than 10 years in 43.4% of British and 68% of Kuwaiti respondents. The majority of British respondents (56.5%) reported the disease severity to be moderate, while the majority Kuwaitis was mild (72%). The annual relapse rates in Kuwait were relatively low with 82% of the Kuwaiti sample had one relapse per year, compared to the 64.5% of British. The most common symptoms reported by British respondents were balance (75.8%), fatigue (74.2%), and weakness (71%), and by Kuwaiti respondents were fatigue (86%), balance (76%), and weakness (66%). The help and support for MS was by far more diverse for the British than Kuwaiti respondents. Before being diagnosed with MS, the majority of British respondents (75.8%) used to engage in different types of physical activities and sports, while only 24% of Kuwaiti respondents were involved in such activities. Even after being diagnosed with MS, 67.7% of the British sample showed determination to remain physically active in comparison to 14% of Kuwaitis.

Discussion

The results unveiled marked differences between two groups of British and Kuwaiti MS patients in terms of patients' age and disease duration and severity. The overwhelming majority of Kuwaiti patients are young individuals who have been with the disease for a relatively short period of time and their MS in most cases was mild. On the other hand, British patients were relatively older, many have been with the disease for a long period of time, and their average MS condition was more serious than that of their Kuwaiti counterparts.

The main support in Kuwait comes from the neurologist, who primarily prescribes medications and advises patients to try to be active. The Kuwaiti respondents thought that lack of encouragement was the main reason for them not exercise. Aptly put, if they try to exercise, they will be discouraged by the loved ones lest the worse happens. On the other side, British patients are generally aware of the benefits of physical and mental health-promoting activities, they can seek help from a wide range of professionals and are more

Severe Psychosis is One of The Rarest CADASIL Manifestations

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Objective:
We present a rare clinical case of a 70-year-old man with CADASIL. It illustrates the challenge clinicians face while diagnosing and treating a patient with severe polymorphic psychosis.
Method:
Clinical case Clinic:
A 70-year-old patient was admitted to our psychiatric hospital for severe polymorphic psychosis. Medical history: Severe headaches and dizziness, epileptic seizures, forgetfulness, became suspicious, occasionally inquiring how to buy a gun.
On examination, he was confused, uncooperative, psychomotorically agitated, saying " I'm admitted to the angel`s department for treatment", "I'm waiting for the jet fighters``, "I am very rich" and that "medicine is just a performance". He felt like blood was being taken from him, that the blood was being sold. Skin biopsy results: nonspecific degenerative changes in blood vessels, which is very characteristic of a CADASIL diagnosis. MRI: probable CADASIL syndrome. The patient was treated with tab quetiapine 75 mg/d , sol haloperidol 1.5 mg/d, tab coaxil 37.5 mg/d.
Results:
The patient significantly improved: within 9 days, the psychosis disappeared. Only asthenic-depressive syndrome and cognitive decline below the level of dementia persisted.
Conclusion:
The clinical manifestations of CADASIL can vary widely. In our case, symptoms occurred late and were non-specific. Severe psychotic symptoms, as seen in our case, according to the literature develop in only about 2% of all cases. The lack of anamnestic data that points toward hereditary transmission causes diagnostic difficulties. Although there is no specific treatment for this disease, early diagnosis remains important, as it helps to manage neuropsychiatric symptoms more effectively.

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Severe Delirium with Symptoms of Catatonia in TB Meningitis and Significant Hyponatremia

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Objective:
We present a challenging clinical case of a 48-year-old man with TB meningitis, history of alcohol dependence and recurrent hyponatremic events, which illustrates the diagnostic difficulties when severe polymorphic psychoses manifests.
Method:
Clinical case Clinic:
The patient was transferred to a psychiatric hospital with severe delirium and significant hyponatremia. During the previous month, he had episodical consciousness disorders, hyponatremia. On examination he was confused and uncooperative. He talked to his dead relatives and felt like he was in a greenhouse. Symptoms of carphology and catatonia were observed as well as meningeal symptoms. Lung radiograph showed disseminated pulmonary TB. The abdominal echo found suspected TB changes in the spleen and adrenal glands. Cerebrospinal fluid: 1 mmol /l glucose, chlorides 105 mmol/l, total protein 2.44 g/l. In the cerebrospinal fluid M. tuberculosis complex DNA was found. He was treated with low doses of antipsychotics, hyponatremia corrected.
Results:
The patient was discharged after 4 days and referred for specific treatment to a TB unit. The patient survived and remained independent.
Conclusion:
Central nervous system TB is rare and is one of the most severe disease forms resulting in death, neurological and mental disorders. Symptomatic mental disorders are nonspecific. They may be associated with both significant hyponatremia and TB neuroinfection itself, which further complicates the diagnostic process. Rapid diagnosis of central nervous system tuberculosis is challenging due to relatively insensitive or slow bacteriological diagnostic methods. Delay in antituberculosis treatment is one of the most important predictive factors of poor outcome.

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Mental Disorders in Neurosyphilis

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Objective:
We present a unique clinical case of a 51-year-old man with neurosyphilis. It illustrates diagnostic and treatment difficulties that arise when severe polymorphic psychosis develops.
Method:
Clinical case Clinic:
Our patient had no previous history of psychosis. He had a history of alcohol abuse and recurrent epileptic seizures. He was also treated for organic depression and organic personality disorder. He was hospitalized when persecutory and poisoning delusions had occurred. Active neurosyphilis was diagnosed. Dynamics: psychosis got severe with emerging delirium and symptoms of catatonia. He was fed by a feeding tube, bedsores developed. We treated him with penicillin and combination of neuroleptics. Psychosis disappeared within 71 days. He was rehospitalised one year later with manifestation of delusions of poisoning, absurd greatness, extreme wealth and hypochondria. The neurologist concluded that previous antibiotic treatment was effective. He was treated with olanzapine up to 10 mg/d and the delusions faded after 139 days, only dementia persisted. MMSE - 24 points.
Results:
Both times the patient significantly improved: psychosis and catatonia disappeared, only asthenic syndrome and cognitive decline persisted. MMSE - 24 points.
Conclusion:
Neurosyphilis can manifest itself in various pathologies. In our case, neurosyphilis exhibited itself by a very polymorphic specter of psychiatric disorders: poisoning, persecutory delusions, delirium state with catatonic symptoms, acute paraphrenic state, organic asthenia, depression, personality disorder and cognitive decline. This clinical picture made diagnostics very complicated. Antipsychotic treatment alone was not effective until antibacterial (etiopathogenetic) treatment was added. Early diagnosis ensures the best outcome for the patient.

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Delirium is One of Covid-19 Disease Faces

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Objective:
We present a successful clinical case of an 85-year-old man who suffered from Covid-19 disease, prostate cancer and was using tramadol for pain management. It illustrates the difficulties of treating severe delirium with self-aggressive behavior.
Method:
Clinical case
Clinic:
An 85-year-old man hospitalized in our psychiatric hospital for suspected suicidal behavior (he was found cutting his throat with a knife). He was diagnosed with a mild form of covid-19 disease, 14 days before the incident. At the time of the incidence his isolation was over for a few days. Severe delirium dominated on examination: the patient was confused, uncooperative, said that he saw three men attacking him trying to get to his throat and cut it, but didn`t succeed. He wanted to complete the attempt himself. The patient was treated with tiapride 200 mg/d, aripiprazole 2.5 mg/d, ac. valproici 500 mg/d., corrected pain management.
Results:
The patient was discharged after 17 days, significantly improved with no delirium, no suicidal thoughts, and critical of former psychotic experiences. Only psycho-organic syndrome with decreasing asthenia persisted. MMSE - 29 points.
Conclusion:
It is very important to acknowledge the serious psychiatric complications that arise during the acute phase of Covid-19 disease. Delayed onset changes in consciousness are not less dangerous, especially in elderly patients with severe, advanced disease. Sometimes delirium lasts longer than the active phase of Covid-19 disease. There is no golden standard of treatment. It is important to use general guidelines for the treatment of somatogenic delirium.

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Glucocorticoids Induced Psychosis

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Objective:
We present a case of a 72-year-old woman with a psychotic episode following prednisolone treatment. She did not have any psychiatric history before. That illustrates the importance of early psychiatric diagnostics in glucocorticoid treatment.
Method:
Clinical case Clinic:
The patient had severe polymorphic psychosis for two weeks, before being sent to our psychiatric hospital. She was on prolonged prednisolone treatment up to 60 mg/day. The patient was euphoric with elevated affect, and said she could predict the future. She stated that the fairies were cleaning her house and anything she touched would glitter. She believed that she could communicate with St. Anthony and felt as if she had resurrected him. She felt like she was in the land of devils and witches, while she herself was a saint, chosen from millions. Treatment with prednisolone was reduced to 20 mg/d. Added antipsychotics: tab quetiapine 50 mg/d sol tiapridal 200 mg/d sol haloperidol up to 5 mg/d.
Results:
The patient was discharged in clear consciousness, fully oriented and critical of the former psychosis after 34 days.
Conclusions:
Glucocorticoids are used to treat a variety of acute conditions. We should not forget that it can provoke severe polymorphic psychosis in addition to a good therapeutic response. Delayed diagnosis still occurs and it is especially important to keep vigilant now. Glucocorticoids are used widely in Covid-19 treatment. Diagnosis hinges on exclusion. The solution is to keep dosages as low as possible, and not prolonging medication regimen beyond what is required.

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IgG Guided Diet Can Decrease Neuroinflammation in Multiple Sclerosis Measured by MR Lesion Load

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Background: Various diets in MS have been reported promising beneficial results, but of poor quality.

Objective: Has an IgG guided diet effect on the progression of brain inflammation measured by quantitative MR?

Methods: 30 RR MS persons were followed in three groups for one year: 1. with immunomodulation with diet, 2. without any immunomodulation with diet, and 3. free group without diet. IgG food intolerance was measured in the 1st, 6th and 12th month by Foodprint*Microarray200+. 3T Siemens Biograph mMR using a protocol with 160 slicesT1 Flash and Flair 3D sequences in sagittal direaction was used. An automated lesion detection was supplemented by a manual detection to demonstrate the MR lesion load (MRLL) at start and at the end of the trial.

Results: All participants ha food intolerance against 2-17 foods. -the average total food immune activity was 3 times higher than those of healthy person`s. 25 out of 30 patients had progression and 5 patients had decrease in MRLL. Those who hold strictly the diet had a decrease in total food immunactivity and less progression in MRLL, and improvement in the neurological status, compared to those, whose diet was not perfect, their total food immuneactivity and the MRLL increased substantially and the neurological status worsened.

Conclusion: The trial demonstrated the IgG guided diet can lower neuroinflammation in RRMS, and the default in the diet worsens inflammation, measured by a quantitative MRLL. IgG tailored diet can further improve the brain inflammation in immunomodulated patients.

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The Role of Inflammation in Psychotic Spectrum Disorders

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Background: Psychotic spectrum disorders (PSD) are disabling and highly prevalent mental syndromes of unknown etiology. PSD onset and progression were shown to associate with cortical thinning and white matter microstructural changes as well as cognitive dysfunction. Both inflammation and neurodegeneration have been proposed as potential mechanisms of PSD.

Objective: To investigate glial changes in PSD using magnetic resonance spectroscopy imaging (MRSI) and test the inflammation hypothesis.

Methods: Whole-brain MRSI was conducted at 3T and used to derive myo-inositol (mIns), n-acetyl aspartate (NAA), choline (Cho), and creatine (Cr) concentrations in 29 patients with schizophrenia or schizoaffective disorder versus 32 healthy control (HC) participants, 18 to 31 years old. Mean metabolite values were obtained for the entire central white matter region and several gray matter regions, including insula and thalamus. Group comparisons were conducted using t-tests with differences considered significant at p0.05.

Results: Significantly increased mIns were observed in the PSD group both as mIns/Cr ratio and in relation to the tissue water content in both white and gray matter regions. In the PSD group, mIns concentration significantly increased with disease duration and was also found to be associated with several cognitive metrics.

Conclusion: Myo-inositol is assumed to reflect glial function and proliferation with increased values considered a proxy for inflammation arising from microglia and/or astrocyte activation or changes. Thus, our results support the inflammation hypothesis of PSD. Further studies employing larger samples are needed to confirm these preliminary results.

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The Macrophage-Specific Histone Deacetylase Inhibitor Tefinostat in X-Linked Adrenoleukodystrophy

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Background:

Cerebral adrenoleukodystrophy (CALD) encompasses a rapidly progressive inflammatory demyelination of the brain, and is the most severe manifestation of X-linked adrenoleukodystrophy (X-ALD), a disease caused by malfunction of the very long-chain fatty acid (VLCFA; C22) transporter ATP-binding cassette subfamily D member 1 (ABCD1). Although in vitro treatment with the epigenetic modifier drug Vorinostat of X-ALD macrophages was found to be beneficial to revert their abnormalities in lipid metabolism, the development of thrombocytopenia limits their use in CALD patients. Since hematopoietic stem cell transplantation can halt the inflammation in CALD, and monocyte-derived macrophages are the most severely affected immune cell types in X-ALD, we propose the use of Tefinostat, a monocyte and macrophage-specific HDAC inhibitor, as a possibly more adequate treatment for CALD patients.

Objectives:

To evaluate in vitro the efficacy of the HDACi inhibitor Tefinostat in macrophages for CALD.

Methods:

Measurement of acetylation levels by flow cytometry to study the specificity of Tefinostat for monocyte-derived macrophages. qPCR to analyze the expression of target genes such as the ABCD1-compensatory protein ABCD2 and other genes involved in lipid metabolism. β-oxidation analysis using labeled VLCFAs to evaluate changes in the peroxisomal catabolism of VLCFAs.

Results:

Our results support the macrophage-specificity of Tefinostat when compared to other immune cells including T and B cells. In addition, Tefinostat induced the gene expression of ABCD2 and other genes involved in lipid metabolism such as the cholesterol efflux transporter ABCG1.

Conclusions:

The macrophage-specificity of Tefinostat, together with the ability of Tefinostat to up-regulate the expression of disease-relevant genes and stimulate the metabolism of VLCFAs, reinforce the importance of studying the possible benefits of the compound for CALD patients as well as for other neuroinflammatory diseases.

References:

Franziska D. Weber et al., 2014

Isabelle Weinhofer et al., 2018

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Higher BDNF Levels in the Circulation is Associated with Angiogenesis, Inflammatory and Metabolic Biomarkers in Children

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Background: Children with obesity have increased risk of T2D, and both are risk factors for neurocognitive deficits. BDNF, which can be released by leukocytes, is critical in neuroplasticity, glucose regulation, fat oxidation, and appetite regulation in adults. Objective: We determined whether plasma BDNF levels is altered in children with obesity, and whether BDNF levels is associated with angiogenesis, inflammatory and metabolic biomarkers. Methods: The study included a total of 77 children and adolescents (aged 5-16 years). Anthropometric and biochemical parameters were measured, and participants were grouped according to their BMI into 3 groups: normal-weight (BMI less than 85th percentile), overweight (BMI between 85th-94th percentile) and obese (BMI 95th and higher percentile). The plasma levels of biomarkers were quantified using ELISA kits. Results: BDNF was directly correlated with VEGF (r=0.6, P0.0001), oxLDL (r=0.5, P0.0001), sST2 (r=0.33, P=0.009), IL-6 (r=0.26, P=0.035), and TGF-β (r=0.8, P0.0001). BDNF was inversely correlated with anti-ox-LDL antibodies (r=–0.3, P=0.014) and thyroxine (T4) (r=–0.35, P=0.014). Children with higher levels of BDNF (3000 pg/ml compared to 3000 pg/ml) had higher levels of VEGF (P0.0001), total cholesterol (P=0.02), LDL (P=0.025), ox-LDL (P0.0001), TG (P=0.055), calprotectin (P=0.055), MCP1 (P=0.028), and TGF-β (P=0.0088), but lower T4 (P=0.0026). There was no difference in the level of BDNF between children with normal weight (n=9) compared to those with obesity (n=9). Males had higher (P=0.015) levels of BDNF compared to females. Conclusion: Higher plasma BDNF levels is associated with angiogenesis, inflammatory and metabolic biomarkers in children.

Neuroimmunomodulation to Accelerate Remyelination in a Murine Model of Multiple Sclerosis

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Background: MS is a debilitating disease, characterized by neuroinflammation and extensive demyelination, particularly as patients age. Current therapies for MS are predominantly immune-modulating but do not directly promote remyelination. Recent research has demonstrated that vagus nerve stimulation (VNS) activates endogenous neuro-immune reflexes that reduce inflammation and are neuroprotective in the CNS (Immunol Rev. 2012 248(1):188).

Objective: To explore potential therapeutic effects of VNS, including accelerating remyelination, in a lysolecithin-induced MS model in young and old mice.

Methods: To induce a self-limited demyelinating lesion, spinal cords of female BALB/c (6 months) or aged C57/BL6 mice (12-19 months) were injected between T3-T5 with 1% lysolecithin (0.5 µL at 0.25 µL/min). VNS (0.75-1 mA) or sham VNS (0 mA) was performed 4 days post-induction, on the day of expected peak lesion volume (J Neurocytol. 1995 24(10): 775). Mice were euthanized on days 8, 10 (aged mice), 14, or 21 post-induction, and spinal cord lesion volumes were quantified from luxol fast blue-stained, 20 µm serial sections.

Results: Remyelination occurred at a significantly accelerated rate in the VNS treated animals. On day 8 post-induction, mean lesion volume in the young VNS group (0.0037 ± 0.0005 mm^3, n=13) was reduced as compared to sham (0.011 ± 0.0016 mm^3, n=12) and the area under the curve from Day 4 through Day 21 was reduced by 65%. Similarly, in aged mice, the VNS group had significantly reduced demyelinated volume (0.02 ± 0.003 mm^3, n=9) than the sham group (0.04 ± 0.004 mm^3, n=9) on Day 10.

Conclusion: VNS accelerated remyelination in this murine model, across both strain and age, demonstrating the neuro-protective effect after a single dose of stimulation. This novel neuroimmunomodulation approach for treatment of autoimmune conditions may provide a pro-remyelination treatment option for chronic demyelinating injury in patients with MS.

T-cell Depleted HLA-Haploidentical Hematopoietic Stem Cell Transplantation in a Child with Neuromyelitis Optica.

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Neuromyelitis optica is an immune-mediated disease characterized by a relapsing course, resulting in progressive disability. In children, given the long life expectancy, a disease-modifying treatment could be particularly desirable. Unfortunately, the currently available treatment strategies with this potential are scarce.

Our female patient was diagnosed at the age of 9 years. At onset, she presented bilateral optic neuritis and progressive hyposthenia at the lower limbs. Magnetic resonance imaging (MRI) showed multiple T2-hyperintense lesions in the right frontal subcortical region and corpus callosum, as well as in the cervical and dorsal spine. The positivity of AQP4-autoantibodies confirmed the diagnosis of NMO. She was treated with multiple lines of therapy (including high-dose steroid, azathioprine, cyclosporine, and rituximab), without control of the disease. She experienced several relapses (Longitudinally Extensive Transverse Myelitis or optic neuritis) with annual relapse rate (ARR) of 1.5. In view of this disease course, after extensive discussion with both patient and her parents, it was decided to consider allogeneic HSCT as a potentially curative option. At the time of HSCT, the girl displayed an Expanded Disability Status Score (EDSS) of 6.5. Since an HLA-matched donor, either related or unrelated, was not available, at the age of 15 years, the patient underwent HSCT from the HLA-haploidentical father. On day +7 after transplantation, the patient presented an episode of monocular amaurosis and blurred vision, successfully treated with retrobulbar injection of dexamethasone, plasma-exchange, and high-dose intravenous immunoglobulins. Twenty-four months after HSCT, the patient is in good general conditions, without any sign of GVHD.

The last MRI performed after 2 years from HSCT showed the absence of new lesions, and a significant reduction of preexisting lesions without gadolinium enhancement. Visual evoked potentials to flash stimulation were absent before HSCT, while a low-amplitude N1/P2 response (around 4 μV) was recorded as from 1 year after HSCT and is still persisting. Clinically, the girl did not experience any re-exacerbation of the disease, showing a long-term stabilization. She presented a significant improvement in the EDDS, which is actually equal to 5 with return to walking without assistance. The AQ4 antibodies remained positive with gradual reduction of titers on serial controls up to last follow-up after 24 months.

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Changes in Muscle Metabolism Measured by MRS in Patients with Multiple Sclerosis

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Background: Mitochondrial dysfunction in the CNS has been demonstrated in many studies in multiple sclerosis (MS). Carnitine (AC), which acts as essential component in mitochondrial energy production and improves fatigue resistance and muscle carnosine is related to contractile function.

Objective: The aim of our study was to analyze the dynamic changes of skeletal muscle lipid accumulation (IMCL), carnosine and AC in rest and exercise in MS patients.

Methods: We compared 9 newly diagnosed MS patients (3M/6F, age 29.1±7,0 yrs., BMI 21.1±3,9 kg/m^2, average EDSS 1.5 vs. 0.9) with 9 healthy controls (age 29.7 ±8.3 yrs., BMI 21.8±2.2 kg/m^2). Carnosine and AC was measured using 7T 1H MRS and compared these to the measures of skeletal muscle oxidative capacity assessed by dynamic 31P MRS during the recovery from exercise challenge.

Results: Despite comparable IMCL in MS and control, we found prolonged time constant of Phosphocreatine recovery (τ_{PCr}) in SM (43±11.7 vs. 28.2±7.7 s, p=0.005) and similar maximal oxidative capacity (Qmax) (0.41±0.08 vs 0.33±0.13 mM.s^{-1}, p=0.1). MS patients had lower baseline (pre-exercise) carnosine compared to controls (4.26±2.07 vs. 6.38±1.87.; p=0.04), while in AC there was no difference (5.53±3.53 vs. 2.94±1.88; p=0.07). MS patients had also higher skeletal muscle phosphomonoester levels than controls (0.71±0.24 vs. 1.02±0.36 mmol/l) and comparable static and dynamic amount of organic phosphate (Pi) baseline and after exercise.

Conclusion: Our study first time described dynamic metabolic characteristic using skeletal muscle 1H and 31P MRS in MS patients. These results suggest that mitochondrial oxidative capacity could be impaired in MS patients. Lower carnosine and trend to lower AC in MS patients compared to controls could be a sign of lower skeletal muscle insulin sensitivity.

Influence of Vitamin D on T-cell Migration Across the Blood-Brain Barrier

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) with unknown etiology. Besides genetic predisposition, environmental triggers contribute to MS susceptibility. In this context, Vitamin D (VitD) deficiency is proposed as major risk factor in the pathogenesis of MS. Previous studies have shown that VitD has profound immunomodulatory roles and that its supplementation is associated with modulation of T-cell responses in MS. Furthermore, VitD inhibits experimental autoimmune encephalomyelitis, an animal model of MS, by reducing the recruitment of effector T cells into the CNS.
The present study aims to understand the potential role of VitD on the migration of different T-cell subsets across the blood-brain barrier (BBB) into the CNS. Our aim is to determine novel mechanisms triggered by VitD in controlling inflammation and restoring defective immune regulatory pathways in MS.
We first relied on flowcytometry to investigate the effect of VitD on the cell surface expression of adhesion molecules on in vitro activated human CD4+ and CD8+ T cells. Secondly, we assessed the role of VitD in influencing the ability of human T-cell subsets to adhere to different recombinant adhesion proteins of the BBB. Lastly, by employing a human CD34+ cord-blood stem cell derived BBB model, we studied the migration of VitD pretreated T cells across the BBB under both, noninflammatory and inflammatory conditions.
We observed that VitD reduces cell surface expression of a4-integrins on T cells resulting in their reduced adhesion to vascular cell adhesion molecule 1 (VCAM-1), and their reduced migration across the BBB in vitro.
Our results show that VitD regulates the expression of adhesion molecules on human T cells and thus influences their interaction with the BBB. Beneficial effects of VitD in MS may thus be due to reducing T-cell migration across the BBB.

Agmatine Therapeutic Potential in Early Neuroinflammation – the Role of BDNF and SPARC

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Background: Experimental autoimmune encephalomyelitis (EAE) represents an animal model of inflammatory and demyelinating CNS disease, widely used in multiple sclerosis research. Objective: The investigation of exogenous agmatine effect on BDNF and SPARC expression in spinal cord of EAE rats and understanding of agmatine therapeutic potential in early neuroinflammation. Methods: EAE was induced by subcutaneous injection of spinal cord homogenate (0.1 ml per animal) in DA rats, divided into 5 groups: Control - treated by 0.9% NaCl (i.p.), CFA – treated by Complete Frend Adjuvant, EAE13 – animals sacrificed on 13th day post immunization (dpi), EAE20 (sacrificed on 20th dpi), EAE+AGM13 – animals treated by agmatine every dpi and sacrificed on 13th dpi, EAE+AGM20 - treated by agmatine and sacrificed on 13th dpi and AGM - received only agmatine (75 mg/kg b.w. (i.p.)). All animals were clinically scored every day until sacrifice. BDNF and SPARC spinal cord concentrations were determined using ELISA method, while their expression in spinal cord was determined by immunohistochemistry. Results: Agmatine treatment successfully attenuated severe clinical deficit in EAE. In both disease phases, significantly reduced BDNF and SPARC concentrations were noticed in EAE rats (p0.001). Agmatine treatment led to the significant increase of both BDNF and SPARC concentrations and expressions in spinal cord of EAE animals. Conclusion: The obtained results confirm that agmatinergic system may be useful in understanding CNS damage pathogenetic mechanisms and that stimulation of neurogenesis could be one of agmatine protective effect mechanisms. Agmatine could represent the new approach in pharmacological strategies in the treatment of neuroinflammation.

ECN2021

Dysregulated Metabolic and Ion Homeostasis Genes in Multiple Sclerosis Patient Macrophages Correlate with a More Inflammatory State and Reflect Patient Clinical Profile

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In multiple sclerosis (MS), immune cells invade the central nervous system and destroy myelin. Patients show large heterogeneity in both pathological and reparative (remyelination) processes. Macrophages contribute to de- and remyelination, and their role in each process depends on their ability to acquire specific phenotypes in response to external signals. Our hypothesis is that disease- or patient-specific defects in macrophage responses are linked to increased inflammation or lack of neuro-regenerative effects, resulting in higher disability accrual.

To test this hypothesis, monocytes were purified from blood samples from clinically heterogeneous MS patients and healthy controls and were activated *in vitro* to obtain homeostatic-like, pro-inflammatory and pro-regenerative phenotypes. Myelin phagocytic capacity and surface molecule expression of CD14, CD16 and HLA-DR were evaluated with flow cytometry. Transcriptomes were generated by RNA sequencing and analyzed with Weighted Gene Co-expression Network Analysis (WGCNA). Correlation was studied between aspects of functional, clinical and transcriptomic profiles.

We identified differences between macrophages from MS patients and healthy controls that indicated a pro-inflammatory predisposition with a notable increase in chemokine expression, suggesting increased recruitment capacity. This was notably correlated with a dysregulation of metabolic and ion homeostasis genes. Higher proportions of CD16+ sub-populations also indicated a macrophage population similar to that seen in MS lesions. In addition, functional and transcriptomic responses to activating stimuli were reduced in MS macrophages. Inter-patient differences suggested a correlation between macrophage phenotypes and clinical data. Interestingly, the MS-specific phenotype was also exaggerated in untreated patients compared to treated patients.

Our results highlight a contribution of macrophage defects to the inflammatory lesions seen in MS, in a way that reflects patient heterogeneity. Future investigation of individual differences may lead to identification of novel pathogenic contributions and biomarkers.

ECN2021

CD49d Expression on Regulatory T Cells Dictates IFNγ Production in Multiple Sclerosis Patients

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Background & Objective

Peripheral tolerance mainly consists of regulatory T cells (Tregs) suppressing autoreactive effector T cells (Teff) which have escaped central tolerance mechanisms. In autoimmune diseases, including multiple sclerosis (MS), Tregs display a defective suppressive capacity. In MS, where autoreactive Teff are reactivated in the central nervous system (CNS), Treg migration to the site of inflammation is desirable. To date, the migratory behaviour of Tregs in MS is unclear.

Methods

We performed flow cytometry on peripheral blood mononuclear cells to identify the expression of chemokine receptors and adhesion molecules on Tregs (thymus-derived, $CD25^{hi}CD127^{lo}Foxp3^{+}$) and Teff on healthy donors (HD), untreated relapsing-remitting (RR) MS (uRRMS), first-line treated RRMS (flRRMS) and untreated secondary-progressive (SP) MS (uSPMS).

Results

In blood of HD, we found that Tregs have a distinct migratory phenotype compared to Teff, with higher expression of CCR6 and lower expression of CD49d. Using the unbiased FlowSOM algorithm for analysis of high dimensional flow cytometry data, 2 subpopulations of Tregs were identified based on CD49d and CCR8 expression. Looking further into these subpopulations, we found that $CD49d^{+}CCR8^{-}$ Tregs specifically produce IFNγ in MS patients but not in HD. For $CD49d^{-}CCR8^{+}$ Tregs, there was no difference in IFNγ production between HD and MS patients. When analysing Tregs in paired cerebrospinal fluid (CSF) and blood samples of uRRMS patients, we found that $CD49d^{+}CCR8^{-}$ Tregs are highly enriched in CSF while $CD49d^{-}CCR8^{+}$ Tregs are absent in the CSF. CCL20, VCAM-1, CXCL10 and CXCL11, the ligands of CCR6, CD49d and CXCR3, are significantly upregulated by inflamed endothelial cells of the blood-brain barrier.

Conclusion

Taken together, these results show that Tregs use a unique set of adhesion molecules and chemokine receptors to migrate to the CNS during MS and that the expression of CD49d identifies a CNS-homing, IFNγ producing Treg subset in MS patients.

Microglial Interaction with Nodes of Ranvier in Physiological and Pathological Contexts

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Myelination of axons is an essential step to ensure the rapid propagation of action potentials by saltatory conduction, which relies on the nodes of Ranvier, short unmyelinated domains highly enriched in voltage-gated sodium channels (Na_v). In demyelinating diseases such as Multiple Sclerosis, the disruption of Nodes of Ranvier is an early event of the lesions. The disruption of this domains leads to a decreased velocity or a failure of axonal conduction, resulting in functional deficits. Microglia, the resident immune cells of the central nervous system, is a major modulator of myelination (Li et al., 2019; Wlodarczyk et al., 2017) and remyelination processes (Lloyd et al., 2019; Miron et al., 2013). Furthermore, along myelinated axons, the domains where microglia can interact directly with the axolemma are restricted to the nodes of Ranvier.

Our objective was to investigate whether microglial cells contact nodal structures in myelinated and (re)myelinating contexts. Using mouse models *in vivo* and *ex vivo,* including live imaging approaches, we showed that these contacts are stable and increase in a remyelinating context, suggesting a potential impact on repair processes. Using our *ex vivo* model, we further demonstrate that microglial process dynamics is reduced at the site of contact, and depends on neuronal activity. We are presently pursuing this study to, characterize the neuronal signal(s) attracting microglia, and understand the functional impact of this interaction.

ECN2021

IL-10 Promotes Myelin Repair in an Ex Vivo Model of Remyelination and microRNA Signatures of Ex Vivo Remyelination

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Multiple sclerosis is an autoimmune disease characterized by peripheral immune infiltration of the CNS and subsequent demyelination of axons, leading in turn to neuron damage and death. This damage can be repaired, however, via a process of remyelination of previous damaged neurons. The cytokine IL-10 has been shown to promote a micro-environment conducive to myelin repair, however the underlying mechanism remains poorly understood. Remyelination can be modelled ex vivo by application of the demyelinating drug lysolecithin to cultured organotypic cerebellum and brain slice cultures, then applying factors and assessing the extent of remyelination via Immunofluorescent microscopy. We show brain slice cultures were successfully demyelinated using lysolecithin and subsequently remyelination was observed ex vivo. Demyelinated slices were then treated LPS, IL-10 and a combination of both, and we observe a trend towards greater remyelination in brain slices treated with the combination of both stimuli. In brain slices obtained from an Arg2 knockout strain, this observed effect is lost. Arg2 is a target of miR-155, suggesting a mechanism via which miR-155 may mediate the observed LPS + IL-10 effect. Additionally, we conducted an OpenArray for microRNA expression in the myelinated, post-demyelination and remyelinated phases of this model, and identify expression modulation in several microRNAs. We confirm expression of key miRNAs with RT-PCR and also evaluate the expression of miRNA targets and genes of general interest in MS.

ECN2021

Lipid-Specific IgMs Enhance CNS Antiviral Defences: Implications for Progressive Multifocal Leukoencephalopathy in Multiple Sclerosis

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Background:

Synthesis of lipid-specific IgM in the cerebrospinal fluid is associated with a lower risk of Natalizumab-treated multiple sclerosis patients developing progressive multifocal leukoencephalopathy (1); a fatal disease caused by opportunistic infection of the CNS by John Cunningham virus. Therefore, we hypothesised that lipid-specific IgM may induce an antiviral response in the CNS.

Objectives:

To investigate the effect of mouse and human lipid-specific IgM on cells of the CNS.

Methods:

Mouse and human IgMs were first tested in heterogenous murine myelinating cultures, containing all major cell types of the CNS. Further mechanistic studies were conducted in homogenous myeloid cultures and analysed using RT-qPCR (IFN-β and ISGs), immunohistochemistry (main markers and cell types), and plaque assays (virus infections).

Results:

A subset of lipid-specific IgMs induced an antiviral response in CNS cultures, which provided protection against a range of encephalitic viruses. Through pharmacological manipulation of these cultures, microglial-derived interferon-beta was identified as the main mediator of this response, with IFN-β upregulation occurring in a cGAS-STING dependent manner. This observation was replicated in pure microglial cultures and was found to be CNS specific, with bone marrow derived macrophages expressing significantly lower levels of interferon stimulated genes (ISGs) in response to IgM compared to microglia. Upregulation of ISGs was observed in all major cell-types of the CNS suggesting signalling between microglia and surrounding cells results in this antiviral response.

Conclusions:

Our data describes a new mechanism where lipid-specific IgM interacts with microglia leading to an antiviral response specifically in the CNS. Further research into the mechanism of this response may help identify new therapeutics for PML.

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ECN2021

Oncostatin M-induced Astrocytic Tissue Inhibitor of Metalloproteinases-1 Drives Remyelination

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Background. The brain's endogenous capacity to restore damaged myelin deteriorates during the course of demyelinating disorders including multiple sclerosis (MS). Chronic demyelination leads to damaged axons and irreversible destruction of the central nervous system (CNS). Currently, no treatment options are available to establish remyelination. A major focus in the field is therefore to identify key molecules and mechanisms that steer effective remyelination and thus identify new targets for therapy. We have identified different members of the IL-6 class of cytokines as dual mode cytokines that steer neuroinflammatory and reparative processes. We previously reported that one of those members, oncostatin M (OSM) limits demyelination in experimental animal model systems.

Objectives & Methods: Here, we aimed to investigate whether OSM is a crucial driver of the remyelination process and what the related downstream mechanisms are. To do so, a dual strategy was taken. On one hand, OSM was delivered to the CNS using stereotactic delivery of lentiviral vectors that overexpress OSM in toxin induced de- and remyelination models. This was complemented with experiments using OSMRbeta KO strains. To further tease out the underlying mechanisms, in vitro models for OPC differentiation were used in combination with KO models for the downstream mediator TIMP-1. Human translation was sought through staining of post mortem MS lesions.

Results & conclusion: We demonstrated that remyelination was completely abrogated in OSMRβ knock-out (KO) mice while OSM overexpression in the chronically demyelinated CNS established remyelination. Astrocytic TIMP-1 was demonstrated to play a pivotal role in OSM-mediated remyelination. Astrocyte-derived TIMP-1 drove differentiation of oligodendrocyte precursor cells into mature oligodendrocytes *in vitro*. *In vivo*, TIMP-1 deficiency completely abolished spontaneous remyelination, phenocopying OSMRβ KO mice. Finally, TIMP-1 was expressed by human astrocytes in demyelinated multiple sclerosis lesions confirming the human value of our findings. Taken together, OSM and its downstream mediator TIMP-1 have the therapeutic potential to boost remyelination in demyelinating disorders.

ECN2021

Oncostatin M and the Inflamed Blood-Brain Barrier: Reducing Endothelial Cell Activation While Increasing its Permeability

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Background & Objective: Blood-brain barrier (BBB) dysfunction is an intrinsic feature of various neurodegenerative and -inflammatory diseases, including multiple sclerosis (MS). Oncostatin M (OSM), a member of the interleukin-6 family, is present in MS brain lesions and its expression is elevated in peripheral blood mononuclear cells of MS patients. We previously demonstrated that OSM exerts neuroprotective and remyelination-promoting functions. However, its specific function in neuroinflammation and BBB integrity is poorly understood. Therefore, we hypothesize that OSM reduces BBB activation and improves BBB tightness during inflammation.

Methods: Primary mouse brain microvascular endothelial cells (mBMECs) and the human cerebral microvascular endothelial cell line (hCMEC/D3) were treated with 25 ng/ml OSM under control and inflammatory conditions. BBB activation was quantified based on cell adhesion molecule and chemokine expression using flow cytometry, a human chemokine array and ELISA, respectively. BBB integrity was quantified by tight junction expression and transendothelial electrical resistance (TEER) measurements over time.

Results: OSM counteracts BBB activation by significantly downregulating intercellular cell adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) protein expression on mBMECs, and VCAM-1 protein expression on hCMEC/D3 cells after an inflammatory stimulus *in vitro*. Moreover, OSM reduces the endothelial expression of various chemokines during inflammation (fractalkine, CCL5, CXCL9, CXCL10, CXCL11), all involved in the recruitment of T helper 1 cells. Herein, a reduced CCL5 secretion by hCMEC/D3 cells and CXCL10 production by mBMECs during inflammation is confirmed by ELISA. In contrast, OSM reduces TEER of mouse and human BBB-ECs under control and inflammatory conditions *in vitro*, associated with decreased claudin-5 tight junction expression.

Conclusion: Together, these data suggest that OSM decreases immune cell attraction by reducing EC activation, while contributing to an increased BBB permeability during inflammation. Additional *in vivo* experiments will elaborate the role of OSM during neuroinflammation.

Genetic Polymorphisms Of Vitamin D Receptors as Prediction Factors for Multiple Sclerosis in Serbian Population

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Introduction: Multiple sclerosis (MS) is a chronic, autoimmune demyelinating disease of central nervous systems in young adults. Vitamin D and single nucleotide polymorphisms (SNPs) in vitamin D receptor (VDR) gene are potentially involved in the pathogenesis of MS. Vitamin D realized its immune-modulatory effects by binding to receptor (vitamin D receptor - VDR), which has several single-nucleotide polymorphisms variants. The aim of this study was to examine the possible associations of FokI, BsmI, ApaI, and TaqI SNPs with

Material and Methods: The study included 90 MS patients, mean age 40.08 ± 12.12 years. The control group consisted of 89 healthy persons blood donors mean age 46.81 ± 16.78 years. Genetic testing was performed at the Laboratory for Functional Genomics and Proteomics Scientific-Research Center for Biomedicine, Faculty of Medicine Niš. Screening of VDR SNPswas performed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method.

Results: The obtained results showed statistically significant differences in the distribution of *FokI* genotypes and alleles between patients and control group ($p = 0.004$ and $\chi 2 = 11.59$; $p = 0.001$). There was a statistically significant difference in the distribution of genotypes *BsmI*polymorphism in MS patients compared with healthy subjects ($p = 0.028$). The frequency of allele BsmI polymorphism showed no statistically significant difference between MS patients and healthy controls ($p = 0.341$). The *TaqI*and *ApaI* genotype distribution were not significantly different between MS patient and controls.

Conclusion: FokI and BsmI polymorphism of the vitamin D receptor are associated with MS. There is a higher frequency of f allele in MS patients, while BsmI B allele is not associated with MS.

ECN2021

Plasticity Between FoxP3+Treg and FoxA1+Treg Cells on Treatment with IFN-beta

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Background

FoxP3+ regulatory T (Treg) cells and FoxA1+Tregs are key in suppressing autoimmunity. However, FoxP3+Treg function is compromised in multiple sclerosis (MS), but proposed to be restored by IFNb treatment. On the other hand, MS patients' positive response to IFNb therapy is associated with generation of anti-inflammatory FoxA1+Tregs. We hypothesized that IFNb induces plasticity in FoxP3+Tregs by reprogramming them to the FoxA1+Treg cell fate.

Objectives

We aimed to investigate if FoxP3+Tregs and FoxA1+Tregs belong to distinct Treg lineages, and if IFNb induces plasticity of FoxP3+Tregs by resuming the genetic signature and features of FoxA1+Tregs.

Methods

We used a high-throughput approach, combining RNA-seq, ChIP-seq, and mass-spectrometry with FACS analysis of human FoxP3+Treg subsets to identify the global plasticity events induced by IFNb.

Results

FoxP3+Tregs and FoxA1+Tregs constitute distinct lineages of T regulatory cells. All of the various human FoxP3+Treg subsets showed plasticity and acquired the FoxA1+Treg transcriptomic, genetic, and phenotypic signatures on treatment with IFNb, including PD-L1 expression. IFNb induced ISG15 and the ISGylation of FoxA1, the lineage-specifying transcription factor of FoxA1+Tregs. FoxA1 upregulated FOXA1, PDL1, TRAIL, STAT2, CD69, CD2, CD48, and ISG15—the FoxA1+Treg signature genes—in FoxP3+Tregs. Finally, FoxA1 bound to enhancer regions of FOXP3, and to TGFB1/3, and TGFBRI, effecting the repression of TGFb signaling in FoxP3+Tregs.

Conclusion

FoxP3+Tregs and FoxA1+Tregs constitute distinct Treg cell lineages. FoxP3+Tregs acquire a FoxA1+Treg transcriptomic, genetic, and phenotypic signature by IFNb signaling. Our study is the broadest analysis of the human Treg profile to date and serves as an excellent resource for understanding Treg biology and plasticity.

ECN2021

IFN-beta, not IFN-alpha, Induces a PD-L1hi FoxA1+ T Regulatory Signature

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Background

FoxA1+Treg cells, a distinct population of regulatory T (Treg) cells, were identified in multiple sclerosis patients responding to interferon-beta (IFNb)-treatment. On isolating FoxA1+Tregs from inflamed brains during recovery and good IFNb-responders among multiple sclerosis patients, we have shown that IFNb-induced FoxA1+Tregs suppress brain inflammation via programmed death ligand (PD-L)1.
Yet, the molecular regulation of Pdl1 by IFNb and FoxA1 in T cells is unknown.

Objectives

We aimed to identify the molecular mechanism by which IFNb and FoxA1 controls PD-L1 expression in T cells, which is crucial for their anti-inflammatory function.

Methods

We used RNA-seq to characterize the global transcriptomic IFNb-induced cell fate changes in FoxA1+Tregs. We used molecular and cellular techniques – luciferase reporter assays, electrophoretic mobility shift assays (EMSA), co-IP, FACS – to address the molecular events leading to Pdl1 gene activation in FoxA1+Tregs during cell fate commitment.

Results

We report the first transcriptomic profile of human FoxA1+Tregs—induced specifically by IFNb, not IFNa, and defined by robust FOXA1 and PDL1 expression. On identifying the 60-bp minimal Pdl1 promoter, we determined that FoxA1 binds to a 27-bp segment within it to drive PD-L1 expression synergistically with IFNb. This activation was potentiated by IFNb-induced phosphorylation of STAT1/2, allowing them to complex with FoxA1, translocate to the nucleus, and bind Pdl1.

Conclusion

Our data characterize the key molecular players and essential sequences in the Pdl1 promoter required for PD-L1 regulation, a central protein for FoxA1+Treg cell fate determination and suppressive function. These hold strong promises as potential therapeutic targets in T cells to achieve anti-inflammatory properties.

ECN2021

Applying iPSCs to Study Microglia Proliferation in Vitro

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Background

Microglia are the innate immune cells of the central nervous system (CNS) and have several well characterised homeostatic functions which help maintain normal physiology. Alterations in microglia phenotype and subsequent neuroinflammation are hypothesised to be a driving factor in progression of numerous neurodegenerative diseases. iPSCs have revolutionised medical research by providing a method to model human diseases with human cells of specific lineages. Previous attempts to establish iPSC-Microglia cell models have either resulted in cells which lack the ability to proliferate or required TGFb to induce proliferation [1,2]. We set out to create an *in vitro* model of iPSC derived microglia in the absence of the anti-inflammatory TGFb.

Objective

Develop a scalable, human iPSC-Microglia model that proliferates in a similar manner to what occurs *in vivo*.

Methods

Microglia precursors were generated using a protocol previously described by Haenseler et al (2017)[1] with minor modifications. Robust differentiation of microglia precursors to microglia was achieved using MCSF, IL34 and N2 supplement with a defined feeding schedule.

Phenotypic characterisation of microglia was performed using immunocytochemistry and flow cytometry. Proliferation, survival and phagocytosis were monitored using the Incucyte Zoom and IL-6 levels quantified using an ELISA.

Results

iPSC-Microglia were produced at scale and characterised using well defined markers of microglia including IBA1, TMEM119, P2RY12, and HLA-DR. Microglia numbers doubled over 72 hours and were dependant on MCSF concentration. Treatment of microglia with lipopolysaccharide altered the growth profile of microglia and resulted in an increased secretion of IL-6.

Conclusion

We have established a robust method to produce viable proliferating microglia from iPSCs, in the absence of TGFb, which respond to inflammatory stimuli.

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Characterization of T Lymphocytes in the Neuroinflammatory Process in SOD1 Mouse Models of Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is an adult-onset progressive neurodegenerative disease characterized by loss of upper and lower motor neurons in the brain and spinal cord (1). Accumulating evidence suggests that ALS is not a neuronal cell- or brain tissue-autonomous disease (2). For instance, T lymphocytes were observed in spinal cords of ALS patients and SOD1 mouse models of ALS (3) along with the presence of autoantibodies (4) and dysregulation of cytokines (5,6) and circulating lymphocytes (7–9). These studies suggest a significant immune component in ALS that is yet to be explored. Along with our recent observations demonstrating the reorganization of CD4 T-cell compartment with aging (10), in this study we interrogate the CD4 T-cell population structure during disease progression of late-onset SOD1G37R and early-onset SOD1G93A mouse models. Using multicolor flow cytometry, we show increased frequency of effector and exhausted T cells in the spleens of SOD1G37R mice as compared to age-matched non-transgenic mice. Furthermore, spinal cords of both SOD1G37R and SOD1G93A mice exhibit a marked infiltration of effector CD4 T lymphocytes expressing the chemokine receptors of Th1 and Th17 cells and CD8 T cells. Overall, we suggest that the significant recruitment of CD4 T-cell subsets into the spinal cord along with their age-related inflammatory properties may indicate a chronic inflammatory response that aggravates the disease process and can be therapeutically targeted.

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ECN2021

Anti-Neuroinflammatory and Neuroprotective Potential of Curcumin Analogues Against Soluble Amyloid β Oligomers

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Background. Extracellular deposits of amyloid β (Aβ), the major pathological hallmarks of Alzheimer's disease (AD), directly cause neuronal damage and death. However, Aβ aggregates bind to pattern recognition receptors on microglia and trigger an inflammatory response, which contributes to exacerbate neuronal damage and the disease progression and severity. Curcumin, a natural polyphenol, is emerging as a potential drug candidate due to its capability to affect multiple key pathways involved in AD, including microglia activation and neuroinflammation.

Objective. Our aim was to identify novel curcumin analogues able to modulate microglia-mediated neuroinflammation in AD.

Methods. Low and high molecular weight Aβ oligomers (LMW AβO and HMW AβO, respectively), separated by capillary electrophoresis and isolated by ultrafiltration, were used to test the inflammatory response of primary microglia and the effects of two more lipophilic analogues of curcumin (Cur6 and Cur16), by measuring the production and release of TNF-α and IL-1β. The possible neuroprotective effect of the tested compounds was studied in primary neurons treated with conditioned medium of microglia exposed to AβO.

Results. The release of TNF-α and IL-1β and the intracellular concentration of IL-1β increased in response to stimulation with HMW AβO, starting from 6 h. In contrast, LMW AβO failed to induce an inflammatory response in microglia cells. Curcumin and its two analogues suppressed the HMW AβO-induced microglia inflammatory response. HMW AβO induced a late neuronal cell toxicity and morphological changes, which were not suppressed by curcumin and its analogues. Finally, conditioned medium from HMW AβO-treated microglia exerted an early toxicity in neuronal cells, which was suppressed by curcumin and its analogues.

Conclusion. These findings allowed us to identify novel lipophilic curcumin analogues able to protect neurons against cytotoxicity in AD by promoting a microglia protective phenotype.