ADITUM Journal of Neurosurgery and Neurology Research

Open Access Research Article

Multiple Sclerosys and the Turing Machine Detoxicant Approach: how Acting on the Common Final Phases of the Pathologic Process can be Relevant.

Luisetto M [1*], khaled Edbey [2], Nili Behzad Ahmadabadi [3], Fronzi P [4], Mashori G. Rasool [5], Yesvi A.R [5], Oleg Yurievich Latyshev [7]

[1] Applied pharmacologist, Environmental Toxicology IMA ACADEMY italy 29121

[2] professor University of Benghazi dep of chemistry

[3] Innovative Pharmaceutical product development specialist, USA

[4] independent researcher Italy

[5] Professor of pharmacology, Department of Medical & Health Sciences for Woman, Peoples University of Medical and Health Sciences for Women, Pakistan

[6] Founder and President, Yugen Research Organization; Undergraduate Student, Western Michigan University, MI, USA 49008

[7] Ima President Ru

Article Info

Received: February 22, 2021
Accepted: February 25, 2021
Published: March 01, 2021

***Corresponding author:** Mauro Luisetto, Applied pharmacologist, Environmental Toxicology IMA ACADEMY Italy

Citation: Luisetto M, Edbey k, Nili B Ahmadabadi, Fronzi P, Mashori G. Rasool. "Multiple Sclerosys and the Turing Machine Detoxicant Approach: how Acting on the Common Final Phases of the Pathologic Process can be Relevant.". J Neurosurgery and Neurology Research, 2(1); DOI: http;//doi.org/03.2021/1.1008.

Copyright: © 2021 Mauro Luisetto. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Aim of this work is to verify some relevant relationship between MULTIPLE SCLEROSYS and a detoxicant strategy in order to fight this severe disease.
It is also verified the oxygen role played in this condition.
In this work some metabolic- vascular and MS relationship are reported .
The same in introduction a dissertation related some worsening factors for MS Under a social science point of view. (how social science can help also in better understanding neuroinflammatory pathology).

Key Words: multiple sclerosys; detoxicant strategy; toxicology approach; oxygen metabolic -catabolic role Genetic; endogen and environmental factors; latitude; immune system; diet; stress; ischemic damages; latitudes; uric acid and purine methabolism; social science

Introduction

By Oleg Yurevich Latushev: some consideration, paradox and dilemma in narrative way: Consideration about uric acid metabolism, environmental factors , diet and other habits can influence in this neuroinflammatory condition.

"Multiple sclerosis in opposition to gout One of the quality blockers of the development of multiple sclerosis is uric acid, Several recent studies have reported lower levels of uric acid (UA), a major scavenger of reactive nitrogen specie [1].

Accordimng :Curr Top Microbiol Immunol . 2008

Role of uric acid in multiple sclerosis S Spitsin 1, H Koprowski:

"In the past decade, a growing number of evidence has implicated free radicals in a variety of patho- physiological conditions including aging, cancer, and the coronary heart- disease. Analyses of different aspects of multiple sclerosis (MS) pathology with respect to oxidative damage have also revealed evidence of free radical injury to the central nervous- system (CNS), although attempts to protect the CNS using various antioxidants have met with only moderate success. Several recent studies have reported lower - levels of uric acid (UA), a major scavenger of reactive nitrogen species, in MS- patients, while other studies found no such correlation. Here, we discuss these studies as well as current efforts to manipulate serum UA levels in MS patients."

(But we must pay attention: blood level not mean local tissue presence.)

However, it also causes gout.

From Gout Culprit to MS Treatment?By Science News StaffMar. 19, 1997 , 12:00 AM

“Gout and multiple sclerosis (MS) may seem worlds apart, but researchers may have found a beneficial connection between the 2 disorders. A new study indicates that uric acid--a compound that builds up in tissues in people with gout--prevents paralysis and death in mice with lesions resembling those seen in human MS. People with MS--a mysterious degenerative condition characterized by muscle weakness and, in advanced cases, paralysis and mental problems--have nerve-cell lesions in the brain and spinal cord containing high levels of the neurotransmitter nitric -oxide (NO). Thinking that high concentrations of the corrosive NO might play a role in the nerve damage, Hilary Koprowski and his colleagues at Thomas Jefferson University in Philadelphia tested in mice three compounds--uric acid, PTIO, and D609--that are known to scavenge NO or inhibit its production.

They first injected a fragment of myelin protein into the brains of the test mice, causing nerve damage similar to that seen in MS patients. Normally, paralysis sets in within 2 weeks, and the mice die within 3 weeks. Koprowski's group found that daily injections of 20 milligrams of uric- acid prevented paralysis in the mice; the other drugs warded off paralysis for only a few days. Some scientists speculate that low uric acid levels may even play a role in the disease. "The idea that a decrease in some normal chemical in the body could cause MS is a new concept," says neurologist M. Rostami of the University of Pennsylvania.”

Thus, for every person who is accustomed to working hard and hard, at all costs, in stressant condition (a potential factor in develop MS) a seemingly inevitable dilemma and paradox arises: multiple sclerosis or gout (related the role played by uric- acid). Can you go beyond this unattractive dilemma? It seems to us that this is possible. Even if a person has a genetic predisposition to these diseases.

First, you should create more gentle conditions for the work of his brain. Secondly, it is necessary to maintain a balance between mental and physical labor. Thirdly, for the brain and spinal cord, as well as for the joints of a hard working person, active versatile nutrition is needed. It consists of high-quality, fresh and well-balanced food products, active stay in the fresh air as much time as possible every day, regardless of the season. If there is an opportunity to walk to and from work on foot or any part of it, then it is better to choose the sunny side of the street.

At the same time, endogenous vitamin D, which prevents the development of multiple sclerosis. Will be generated more efficiently.

See Iris Marin Collazo, M.D. 2020 mayo clinic
“Research over the years has shown that maintaining adequate levels of vitamin D may have a protective- effect and lower the risk of developing multiple- sclerosis (MS). A number of studies have shown that people who get more sun exposure and vitamin-D in their diet have a lower risk of MS.”

Along with this, the level of consumption of exogenous vitamin D will increase. During such a walking walk, if possible says Latishev , give preference to those streets along which there is the least amount of traffic and whose gas pollution is naturally lower. The noise level and the risk of collisions with vehicles when crossing the road along a pedestrian crossing are lower here - both of these factors should also be attributed to stress-forming factors. Indeed, although this requires more evidence, stress is also ranked among the set of risk factors for the onset of multiple sclerosis [2].

Lancet Neurol 2004

Environmental risk factors in multiple sclerosis aetiology Ruth Ann Marrie“The epidemiology of multiple sclerosis (MS) has been intensively studied. It is conceptualized as a complex disease in which genetic and environmental -factors act together to cause disease. There are temporal and geographic variations in disease-risk, and risk of disease may be affected by migration between regions of differing risk. Numerous potential causal factors including infection, immunizations, physical and the emotional stressors, climate, diet, and occupational exposures have been studied using various observational study designs. Thus far, no single environmental exposure has been consistently identified as a causal- factor in MS, but sufficient data have accumulated that causal pathways should be postulated and tested. This review will focus on the environmental- epidemiology of MS.”

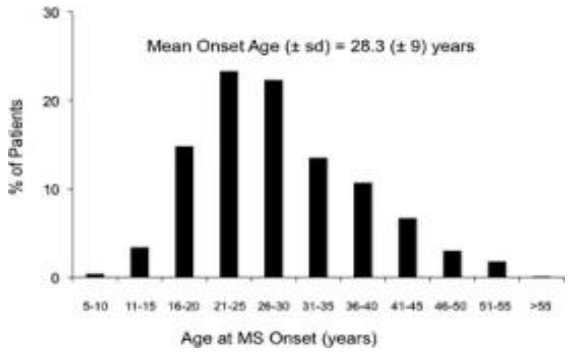
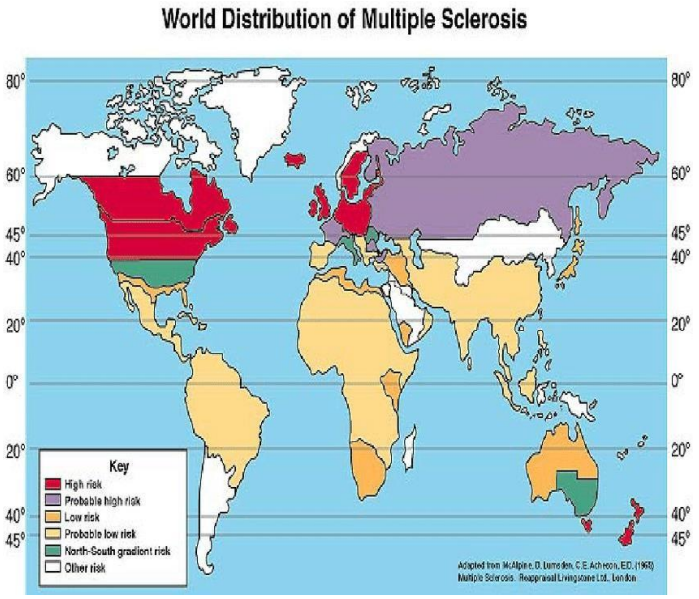


Figure n 1: Age onset MS

If the predisposition of the human brain and spinal cord to the development of multiple- sclerosis has already been established by doctors, he should think about changing his place of residence.

First of all - to choose a more southern geographical latitude for permanent residence.



According nature nature reviews neurology research highlights article November 2016

Multiple Sclerosis

Latitude and vitamin -D influence disease course in multiple sclerosis Heather Wood
Nature Reviews Neurology volume 13

"The researchers found that age of MS onset was, on average, 2 years earlier among individuals living in higher latitudinal regions (50.0–56.0°) than in those living at lower- latitudes (19.0–39.9°)". And preferably say Latishev in the countryside to avoid stressant-condition . This will allow avoiding a significant number of associated environmental risk- factors. So it is actually stressful.

If, due to a number of circumstances, it seems difficult or completely impossible to perform such an act, then avoiding the next negative- factor entirely depends solely on the degree of development of a person's willpower. It's about smoking.
See article : Smoking: effects on multiple sclerosis susceptibility and disease progression Dean M. Wingerchuk 2012
"Multiple -sclerosis (MS) is associated with both genetic and environmental factors that influence disease susceptibility. Exposure to cigarette- smoke is emerging as a viable environmental risk factor for MS that contributes to both increased disease susceptibility and more rapid disease advancement. The relative- risk for MS development is approximately 1.5 for smokers compared with nonsmokers. there may be important interactions between smoking, an individual's genetic- background, and other environmental risk -exposures.
This review summarizes the current evidence supporting the association of smoking with MS risk and disease course, with additional comments on causation."

If the reason for smoking is the body's need for acute and extraordinary sensations, then at present there are a number of other long-standing ways to realize their frank whims of this kind. If a smoker seeks in this way to demonstrate his alleged independence, elegance, style, etc., then in any of these cases a cigar or cigarette is not a non-alternative way of self-expression in one way or another. As the need to preserve one's health becomes more relevant, one can think about which adequate and definitely more more positive substitute should be given preference. In addition, an increasing number of countries around the world are making efforts to depopulate- smoking. These are anti-advertising, and laws on the prohibition of smoking in public places, and the encouragement of non-smoking employees in organizations and institutions, special bonuses. Or, on the contrary, restrictions are imposed on hiring or career development for smoking- employees. Smoking is both a direct and an indirect factor in the onset of multiple sclerosis. In a direct meaning, smoking pollutes the blood flowing to the white matter of the brain and spinal cord, which interferes with the normal metabolism in the brain tissue. In an indirect sense, smoking leads to the development of another terrible disease in a person. hepatitis B, vaccination of which seem involved also in the development of multiple sclerosis most likely [3, 4].

According an article in Neurology 2004.
Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study Miguel A Hernán et al : " A potential link between the recombinant hepatitis- B vaccine and an increased risk of multiple- sclerosis (MS) has been evaluated in several studies, but some of them have substantial methodologic limitations.
The authors conducted a nested case-control study within the General Practice Research- Database (GPRD) in the United Kingdom UK . The authors identified patients who had a first MS diagnosis recorded in the GPRD between Jan 1993 and Dec 2000. Cases were patients with a diagnosis of MS- confirmed through examination of medical -records, and with at least 3 years of continuous recording in the GPRD before their date of first symptoms (index- date). Up to 10 controls per case were randomly selected, matched on age, sex, practice, and date of joining the practice. Information on receipt of immunizations was obtained from the computer records. Results: The analyses include 163 cases of MS and 1,604 controls. The OR of MS for vaccination within 3 years before the index date compared to no vaccination was 3.1 (95% CI 1.5, 6.3). No increased risk of MS was associated with tetanus and influenza- vaccinations.

These findings are consistent with the hypothesis that immunization with the recombinant hepatitis- B vaccine is associated with an increased risk of MS, and challenge the idea that the relation between hepatitis B vaccination and risk of MS is well understood." And although the WHO seeks to deny this detrimental effect of this vaccination, and of any vaccinations in principle [5], we do not consider ourselves entitled (say latyshev) to completely refuse to classify this influence as a factor in the development of multiple sclerosis. The psychosomatics of multiple sclerosis should also be taken into account [6].

See Body Psychotherapy in Progressive and Chronic Disorders Editor(s): Ventling, C.D. (Basel)
Multiple Sclerosis: The Psychosomatic Consequence of Unsuccessful Bonding A Viewpoint Munzel M.
Ventling CD (ed): Body Psychotherapy in Progressive and Chronic Disorders.Basel, Karger, 2002 As mentioned above, a smoker can become the object of this disease with a high

probability. Many also smoke because they feel insecure in themselves, strive to extinguish the feeling of internal-discomfort, a sudden irritation. such attempts never bring lasting results. In this way. A psychological problem that has not been resolved once, takes root and is aggravated by the addition of additional nuances, which also negatively affect the state of the body. if a person with a predisposition to developing multiple-sclerosis has experienced the loss of a loved one, this can affect the progression of the disease in 2 ways.
First, stress will be experienced, which was already mentioned above among the primary negative factors. Secondly, the psychosomatic model itself comes into play, according to which the destruction of the myelin substance occurs at the site of the "projection" of established conditioned reflexes and emotional connections.

Acta Radiol . 2016 Mar.

Limbic pathway lesions in patients with multiple sclerosis

Neslin Sahin et al "A relatively high frequency of lesions involving the limbic- tracts may explain memory deficits and emotional dysfunction commonly experienced by patients with MS. The combined information from T2W, FLAIR, and DTI-derived FA color map allowed for more accurate localization of lesions affecting the major white- matter tracts of the limbic system."

The human body thus includes a protective regime, striving, as it were, to erase from its existence those interpersonal relationships that can no longer be reproduced with a sufficient degree of reliability in the future in relation to the untimely lost object of love, reverence, reverence, respect, etc. If such withdrawal does not occur, then the organism as a whole may well be destroyed. Therefore, he "prefers" to sacrifice individual vectors of the myelin -substance, but preserve the nervous system as a whole. Of course, such assumptions require a lengthy and multiple verification.

(Neuroplasticity is the ability of the nervous system to change its activity in response to intrinsic or extrinsic -stimuli by reorganizing its structure, functions, or connections. A fundamenta-l property of neurons is their ability to modify the strength and efficacy of synaptic- transmission through a diverse number of activity-dependent mechanisms, typically referred to as synaptic plasticity, (in evolutive phases this properties are different vs adult or elders) Neuroplasticity is a term used to describe changes to the brain that happen throughout the lifespan in response to the new -experiences.
However, at the same time, it seems difficult to collect anamnesis, since any additional touch on the topic of a breakup, which is painful for a person, for one reason or another in close relationships can also contribute to an additional leap in the development of the underlying -disease.

How can and should we prevent the development of multiple sclerosis manifestations in humans? It should be said unambiguously that it is impossible to create for him an environment in which the desired interpersonal relationships will be preserved once and for all. Moreover, an attempt to do this in itself could be regarded as an invasion of a person's "terra incognita".
However, if he himself decides to turn to a highly qualified psychologist, then the latter is able to help him put these interpersonal relationships in their proper place in the person's system of values. This will help to promote, if not eliminate the prerequisites for the development of multiple -sclerosis in him completely, then at least in some way inhibit the rate and multiplicity of manifestations of this disease in the medium term.

Also, a significant role in increasing the ability of the brain and spinal- cord to resist the development of multiple sclerosis is played by respect for the state of the spinal column, especially its upper part. In this case, the brain will receive adequate nutrition, timely release from its waste products, as well as maintain a reliable immune defense of all its membranes. Maintaining the working- condition of the spine at the proper level is also the focus of attention when the opposite link of the dilemma we have indicated, namely gout, arises. Since it is the source of multiple lesions of the articular surfaces and membranes, we must take into account the articular nature of the spinal- column.

Firestein, an associate professor of cell biology and neuroscience at Rutgers, The State University of New Jersey, and her laboratory team have reported their discovery in the Early View version of the journal Glia. "It is interesting to note that people with gout never seem to develop multiple -sclerosis," Firestein said. "In animal models of multiple sclerosis, the addition of uric acid reduces symptoms and improves prognosisIn spinal cord injury, as well as stroke, two kinds of damage can occur," Firestein explained. "First there is the physical damage, but this is followed by secondary chemical- damage to neurons [nerve cells] by compounds released in response to the trauma. We have found that uric acid can promote an early intervention step in combating this chemical damage through its action on astroglial cells."

Distribution of White Matter Lesions

	Vascular	MS
Corpus callosum	- uncommon	- common
U-fibers	- uncommon	- common
Cortical lesions	- infarction	- sometimes
Basal nuclei	- typical	- uncommon
Infra tentorial	- uncommon	- typical
Temporal lobe	- uncommon	- early involvement
Periventricular	- uncommon	- typical
Spinal cord	- uncommon	- typical
Gd-enhancement	- no	- yes
Dawson fingers	- no	- typical
Distribution	- asymmetric	- symmetric/diffuse

Multiple Sclerosis - Diagnosis and differential diagnosis Frederik Barkhof, Robin Smithuis and Marieke Hazewinkel
"There are multiple lesions in the spinal -cord. This is another typical feature of MS. Typical spinal cord lesions in MS are relatively small and peripherally located.
They are most often found in the cervical- cord and are usually less than 2 vertebral segments in length."
In this case, local baths (for palms and feet), compresses, applications, rubbing, various types of massage that are

permissible for a given state of the human body will come to the aid of the spine, as well as the joints of the lower and upper extremities. Indirectly, but no less effectively, inhalation, rinsing, and acupuncture effects on certain areas of the affected areas can also help. This will create a favorable background for the overall healing of the body, which in this case will no longer have to spend its limited resources to maintain immune- function in the areas adjacent to the affected area. At the same time, the slowly increasing recovery capabilities of the body will be more accurately and more efficiently directed strictly to the required area".

" Now we offer you to consider in what ratio such metabolic disorder as gout acts with multiple -sclerosis.

Clin Biochem 2009 Jul;42(10-11):1001-6. doi: 10.1016/j.clinbiochem.2009.03.020. Epub 2009 Mar 31. Increase of uric acid and purine compounds in biological fluids of multiple sclerosis patients

Angela M Amorini 1, Axel Petzold, Barbara Tavazzi, Judith Eikelenboom, Geoffrey Keir, Antonio Belli, Gavin Giovannoni, Valentina Di Pietro, Chris Polman, Serafina D'Urso, Roberto Vagnozzi, Bernard Uitdehaag, Giuseppe Lazzarino

" In this study, the concentrations of uric- acid, purine profile and creatinine in samples of cerebrospinal fluid and serum of multiple sclerosis (MS) patients were measured by HPLC and compared with corresponding values recorded in patients without MS - (cerebrospinal fluid) and healthy subjects (serum).

All samples were deproteinized with ultrafiltration (which ensures minimal sample -manipulation and efficient protein removal) and then assayed for the synchronous HPLC separation of uric acid, hypoxanthine, xanthine, inosine, adenosine, guanosine and creatinine.

The values of all compounds assayed were significantly higher in both biological fluids of MS patients with respect to values measured in controls. In particular, serum hypoxanthine, xanthine, uric acid and sum of oxypurines were, respectively, 3.17, 3.11, 1.23 and 1.27-fold higher in these patients than corresponding values recorded in controls ($p<0.001$).

Differently from what previously reported, we here demonstrate that all purine compounds, including uric acid, are elevated in biological fluids of MS- patients. Reinforced by the trend observed for creatinine, this corroborates the notion of sustained purine catabolism, possibly due to imbalance in ATP homeostasis, under these pathological conditions. These results cast doubt on the hypothesis that uric acid is depleted in MS because of increased oxidative stress, rather suggesting that this disease causes a generalized- increase in purine catabolism. As observed in other pathological states, uric acid, purine compounds and creatinine, can be considered markers of metabolic energy imbalance rather than of reactive oxygen species, even in MS."

Related uric acid role : hypothesis and difficulties

If we take into account the effect of uric acid in the the spread of atherosclerotic plaques, then we perceive it as an expedient process of reducing the excretion of uric acid by the kidneys and maintaining its concentration in the blood.

However, if the threat of the onset and development of multiple-sclerosis remains high, and the level of uric acid in the blood does not decrease, and the human body faces the threat of a clinical symptom of hyperuricemia.

In turn, over time, this leads to the formation of foci of pathological compaction of subcutaneous tissue, the emergence of the so-called tofuses. In addition to disturbing the aesthetic appearance of various parts of the body, gout is also characterized by severe pain at the site of the formation of tofus.

Therefore, it is in the interests of everyone who has it to irrevocably reduce the level of hyperuricemia as soon as possible.

So Related the previous consideration about some worsening factors :

To prevent the threat of the development of multiple sclerosis from renewing, it is necessary to quickly, by willful effort, radically change the daily stressant routine, diet, and get rid of bad habits as soon as possible.

No matter how attractive they are in practice say Latyshev.

If it in the development of multiple sclerosis is also considered stress factors , according some researcher (see references) , unbearable and incessant intellectual work, such exhaustion should be completely excluded.

If this seems impossible, which most often happens, then it is necessary to divide the existing volume of labor into feasible doses. For this, the stages of work and rest should be alternated more often, which will allow not to overstrain, avoid emotional burnout, and also solve the tasks set for oneself in time and in full.

If this already seems impossible, we should, in our opinion say Latishev , choose a different path. Namely, a person who is afraid of the development of multiple sclerosis should apply his organizational. Not just performing talents.

This will allow him to create a team capable of accurately and on time to complete everything that one performer, for one reason or another, was not able to do. Moreover, by combining the creative vision of the problem being solved, you can get a more interesting, multifaceted, in its own way unique result.

In order to avoid stressant condition If a person at risk of defeat due to multiple sclerosis cannot find the right team of collaborators, he should turn to one of his friends who would help him do this, and would completely take on this noble mission to protect his friend from consequences of the spread of multiple sclerosis.

This will mean that a potential patient will have a kind of manager, whose work will indirectly affect the fate of his health. Thus, there are a number of consistent approaches to solving the problem of physical health and building a reliable and convincing strategy to protect the body from multiple sclerosis.

If no one uses any alternative scenario of taking care of his own health, it is highly likely that he will continue to suffer from stress related disease , only to an increasingly increasing extent.

And then it will already be necessary to apply indirect scenarios - how to avoid risk of neuroinflammatory condition like multiple sclerosis, while at the same time not letting metabolic disease like gout take over your body more and more.(influence of diet , habit and so on).

Alcohol abuse: some consideration:

It is equally important to get rid of alcohol addiction in time - both in the case of the threat of the development of multiple sclerosis,

and in the event of gout. Mainly.

According : 1188 JAMA Neurology September 2014 Volume 71, Number 9 jamaneurology.com Julia Pakpoor, BA at al "This study supports the presence of a significant positive association between alcohol- misuse disorders and MS risk, particularly in men." This concerns the addiction of many inhabitants of the planet to drinking alcohol. Some people reassure themselves that they drink alcohol a little and infrequently, only on holidays or during rare meetings with people who are especially dear to them. But the fact is that neither for the development of multiple-sclerosis. The list of reasons for which alcohol is taken internally does not matter for the progression of gout.

Moreover, the required amount of alcohol is produced and used with the proper set of chemical reactions in the most normally functioning human body. This suggests that any dose of orally ingested alcohol is already deliberately excessive. And almost equally it can lead to the emergence of a weak-willed person - both multiple sclerosis and gouty manifestations. Therefore, it seems wise to us to prohibit the ingestion of alcohol, for example, in some countries in the world tradition. I would like to see such and similar noble traditions adhered to as many inhabitants of the planet Earth as possible to refuse not only from drinking alcohol inside, but also from the abuse of tea and coffee.

According Arthritis Care Research News Alerts
Coffee Consumption May Lower Blood Uric Acid Levels - The Precursor of Gout Arthritis Care Research News Alerts. 2007

"High uric acid levels in the blood are a precursor of gout, the most common inflammatory- arthritis in adult men. It is believed that coffee and tea consumption may affect uric acid levels but only one study has been conducted to date. A new large-scale study published in the June 2007 issue of Arthritis Care & Research(http://www.interscience.wiley.com/journal/arthritiscare) examined the relationship between coffee, tea, caffeine- intake, and uric acid levels and found that coffee consumption is associated with lower uric acid- levels but that this appears to be due to components other than caffeine".

Arthritis Rheum 2007 Jun
Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey Hyon K Choi 1, Gary Curhan "Serum uric acid level decreased with increasing coffee- intake. After adjusting for age and sex, serum uric acid level associated with coffee intake of 4 to 5 and >/=6 cups daily was lower than that associated with no intake by 0.26 mg/dl (95% confidence interval [95% CI] 0.11, 0.41) and 0.43 mg/dl (95% CI 0.23, 0.65; P for trend < 0.001), respectively. After adjusting for other covariates, the differences remained significant (P for trend < 0.001). Similarly, there was a modest inverse- association between decaffeinated coffee intake and serum uric acid levels (multivariate P for trend 0.035). Total caffeine from coffee and other beverages and tea intake were not associated with serum uric- acid levels (multivariate P for trend 0.15). The multivariate- odds ratio for hyperuricemia in individuals with coffee intake >/=6 cups daily compared with those with no coffee use was 0.57 (95% CI 0.35, 0.94; P for trend 0.001)"

Figure n 4: coffea comsumption world

These drinks also contribute to the deposition of uric acid in the human body due to the rather high content of purines in them.
Nov. 11, 2010 (Atlanta) -- An extra jolt or two of caffeine may trigger a gout attack in people with the painful and often disabling arthritic condition, preliminary research suggests.

"We found that overall, as the number of servings of caffeinated beverages increased, so too did the chance of having recurrent gout attacks," says Tuhina Neogi, MD, PhD, associate professor of medicine at Boston University School of Medicine."

In order to painlessly give up, for example, from excessive - consumption of tea, one should replace traditional tea with herbal teas or tea made from one type of medicinal or simply aromatic herb, to which an allergic reaction does not occur in the human body say Latishev.

If you use an infusion of strawberry leaf as tea, then it will rid the body of gout in two ways at once - both at the stage of accumulation of purines and at the stage of excretion of uric acid. This will be the case with almost any diuretic tea. As for coffee, the transition from drinking it to drinking, for example, chicory coffee will provide patients with a double -benefit at the same time. Just as with the rejection of traditional tea, purines will no longer be deposited in the joints. And at the same time, natural coffee that is absent in the diet will no longer promote the leaching of calcium from the bones, which could otherwise make them more fragile.

See article Caffeine intake increases the rate of bone loss in elderly women and interacts with vitamin D receptor genotypes
Prema B Rapuri, J Christopher Gallagher, H Karimi Kinyamu, Kay L Ryschon
The American Journal of Clinical Nutrition, Volume 74, Issue 5, November 2001, Pages 694–700, https://doi.org/10.1093/ajcn/74.5.694

It so happens that the joint itself is strong and strong, but the bone, the end of which it is, has lost a significant amount of calcium in its composition. In this case, a fracture is possible at the site of the transition of the bone surface to the articular one. An example of such a condition is a fracture of the femoral neck, which is

characteristic of people predominantly of the elderly, who have significant excess weight. In connection with the topic we have touched upon here, being overweight also has a definitely two fold negative connotation. In addition to unambiguous compression at the junction of the joint with the bone spine and a significant increase in the likelihood of fracture in this area, excess weight is also a provoking circumstance in the accumulation of purines as a cause of gout due to renal problems.

It should be reported with confidence that excess weight has a negative impact on the development of multiple sclerosis.
Body mass index correlates with multiple sclerosis disease and symptom severity in women, but not in men Richter B Barnabas Health, NJ, USA

Cutter G et al :
"In this cross-sectional study, BMI showed a modest correlation with MS- severity and symptom burden in women. In men, only anxiety score correlated with BMI. Further study is required to determine why BMI has a sexually- dimorphic effect on disease and symptom severity."
Cholesterol plaques, narrowing the lumen of the central and peripheral blood vessels, impede normal blood flow, the flow of nutrients into organs and tissues.

Multiple sclerosis and stroke: a systematic review and meta-analysis Ye Hong, Huai Rong Tang, Mengmeng Ma, Ning Chen, Xin Xie & Li He BMC Neurology volume 19, Article number: 139 (2019)
"ischemic stroke was particularly more common in the MS population than in people without MS [RR = 6.09, 95% CI (3.44, 10.77), P < 0.00001]. Compared with the general population, people with MS have an increased- risk of developing any type of stroke and ischemic stroke in particular. Consistent results were obtained from patients of different sexes and age groups. Preventative- measures and treatments should be administered at earlier time points to improve patient outcomes."

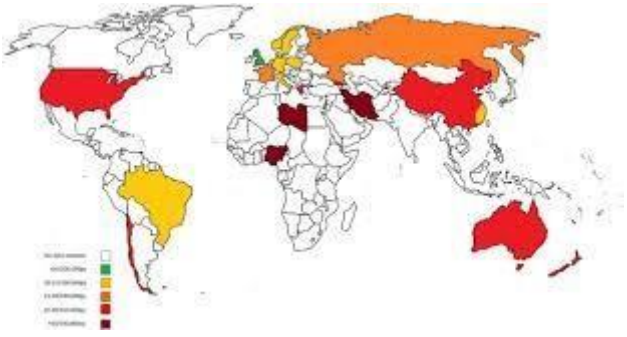


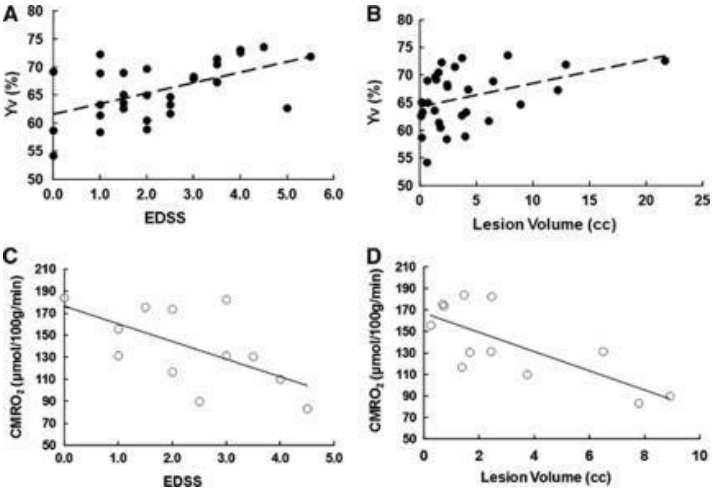
Figure 5: stroke incidence in young adults

And also their timely release from natural waste products of cells of the human body. This inevitably has a bearing on the metabolic- process in the cells of the brain and spinal cord.

Along with a combination of other negative factors, excess weight also contributes to the progression of the detrimental process of replacing the myelin substance with connective -tissue. As a result, the progression of multiple sclerosis becomes more and more pronounced. " (1-6)

Material and Methods
with an observational point of view some relevant literature is analyzed and after the submission to researcher of an experimental project hypotesys it is provided a global conclusion.

Results from literature :
Characterizing brain oxygen metabolism in patients with multiple sclerosis with T2-relaxation-under-spin- tagging MRI
Yulin Ge et al "In this research study, venous oxygen saturation and oxygen metabolic changes in multiple sclerosis (MS) patients were assessed using a recently developed T2-relaxation-under-spin-tagging (TRUST) magnetic resonance- imaging (MRI), which measures the superior sagittal venous sinus blood-oxygenation (Yv) and cerebral metabolic rate of oxygen (CMRO2), an index of global oxygen consumption. Thirty patients with relapsing-remitting MS and 30 age-matched healthy controls were studied using TRUST at 3 T MR. The mean expanded disability status scale (EDSS) of the patients was 2.3 (range, 0 to 5.5). We found significantly increased Yv (P<0.0001) and decreased CMRO2 (P=0.003) in MS patients (mean±s.d.: 65.9%±5.1% and 138.8±35.4 μmol per 100 g per minute) as compared with healthy- control subjects (60.2%±4.0% and 180.2±24.8 μmol per 100 g per minute, respectively), implying decrease of oxygen consumption in MS. There was a significant positive -correlation between Yv and EDSS and between Yv and lesion load in MS patients (n=30); on the contrary, there was a significant negative correlation between CMRO2 and EDSS and between CMRO2 and lesion load (n=12). There was no correlation between Yv and brain atrophy measures. This study showed preliminary evidence of the potential utility of TRUST in global oxygen metabolism. Our results of significant under-utilization of oxygen in MS raise important questions regarding mitochondrial respiratory dysfunction and neurodegeneration of the disease." (7)



Relationship between Yv (the superior sagittal venous sinus blood oxygenation) and expanded disability status scale (EDSS) (A) and lesion volume (B), and between cerebral metabolic- rate of oxygen (CMRO2) and EDSS (C) and lesion volume (D) in patients with multiple sclerosis (MS) patients. A significant positive correlation was observed between Yv and EDSS (r=0.54,

P=0.002) (A) and between Yv and lesion volume (cm3) (r=0.40, P=0.03) (B). In contrast, there was significant negative-correlation between CMRO2 and EDSS (r=−0.61, P=0.03) (C) and between CMRO2 and lesion volume (r=−0.74, P=0.005) (D) in patients with relapsing-remitting MS, suggesting that patients with a higher- venous oxygenation level (Yv) or lower oxygen consumption tend to have higher clinical disability and lesion load.

Inflammation, Iron, Energy Failure, and Oxidative Stress in the Pathogenesis of Multiple Sclerosis Lukas Haider "Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous- system. Different trigger pathologies have been suggested by the primary cytodegenerative "inside-out" and primary inflammation-driven "outside-in" hypotheses. Recent data indicate that mitochondrial- injury and subsequent energy failure are key factors in the induction of demyelination and neurodegeneration. The brain weighs only a few percent of the body mass but accounts for approximately 20% of the total basal oxygen consumption of mitochondria. Oxidative- stress induces mitochondrial injury in patients with multiple sclerosis and energy failure in the central nervous system of susceptible individuals.

The interconnected mechanisms responsible for free radical production in patients with multiple- sclerosis are as follows: (i) inflammation-induced production of free radicals by activated immune cells, (ii) liberation of iron from the myelin sheets during demyelination, and (iii) mitochondrial injury and thus energy failure- related free radical production. In the present review, the different sources of oxidative stress and their relationships to patients with multiple sclerosis considering tissue injury mechanisms and clinical- aspects have been discussed. "(8)

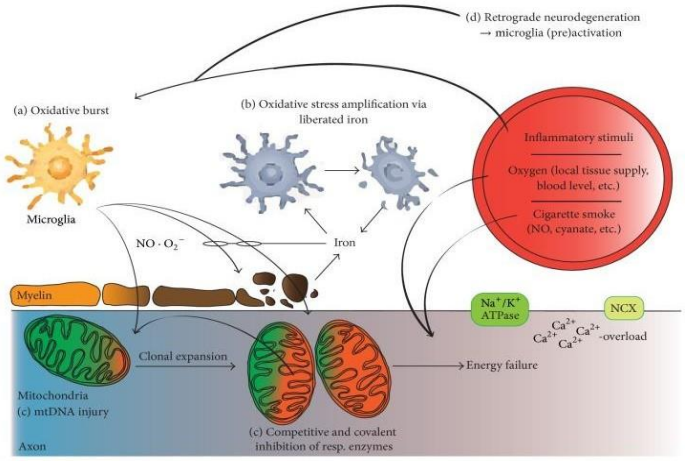


Figure. 7: Oxidative stress-related mechanisms of tissue injury in multiple sclerosis. The temporal sequence and interconnection of cytotoxic events in MS may be different in individual -lesions, stages of the disease, and different patients. Therefore, Figure 1 does not describe a timeline from events depicted in (a) to that in (d). (a) Microglia are activated by an unknown trigger pathology, the breakdown of the blood-brain barrier, and local and systemic inflammatory- stimuli. Microglia activation itself may further impair the blood-brain barrier permeability. Microglia release nitric monoxide and superoxide molecules into the extracellular-space. Nitric monoxide is uncharged and therefore penetrates lipid layers.

Contrary to nitric monoxide, superoxide is unable to diffuse across biological membranes. It is rapidly converted into hydrogen peroxide, which, in contrast to superoxide, is able to diffuse into the extracellular- environment. Additional amplification mechanisms involve microglia preactivation via axonal- degeneration (d). (b) Iron is physiologically stored within the myelin sheets and liberated into the extracellular space upon demyelination. Extracellular- iron amplifies oxidative stress as it travels between the ferrous and ferric states, inducing the production of highly reactive hydroxyl radicals. Iron is absorbed by microglia, which show histological signs of cell death under the high iron load and thus may release iron and initiate a second wave of oxidative stress. (c) Mitochondrial DNA (mtDNA) is vulnerable to free radical-mediated damage resulting in mtDNA deletions, which are found in neurons and axons of patients with multiple sclerosis. Mitochondria carrying such mutations are amplified by the clonal expansion in neurons. The mitochondrial-respiratory chain is inhibited by covalent modifications caused by free radicals both competitively and irreversibly. A combination of these factors leads to energy failure via decreased ATP production. An important source of free radicals is the mitochondrial respiratory chain itself, particularly at low oxygen tension and reperfusion and in demyelinated- axons. The exogenous factors, such as free radicals and cyanate delivered by smoking, inhibit mitochondrial function and cause demyelination in experimental conditions. Energy deficiency lowers Na+/K+-ATPase activity, resulting in the reverse operation of the Na+/Ca2+ exchanger (NCX) and thus increases Ca2+ levels. This event further activates the neurodegenerative and cell death pathways.

Research Paper

Hyperbaric oxygen therapy increases telomere length and decreases immunosenescence in isolated blood cells: a prospective trial

Yafit Hachmo et al:

"Aging is characterized by the progressive loss of physiological capacity. At the cellular- level, two key hallmarks of the aging process include telomere length (TL) shortening and cellular senescence. Repeated intermittent hyperoxic- exposures, using certain hyperbaric oxygen therapy (HBOT) protocols, can induce regenerative effects which normally occur during hypoxia. The aim of the current study was to evaluate whether HBOT affects TL and senescent cell concentrations in a normal, non-pathological, aging adult- population.

Thirty-five healthy independently living- adults, aged 64 and older, were enrolled to receive 60 daily HBOT exposures. Whole blood samples were collected at baseline, at the 30th and 60th session, and 1-2 weeks following the last HBOT session. Peripheral blood- mononuclear cells (PBMCs) telomeres length and senescence were assessed.

Telomeres length of T- helper, T cytotoxic, natural killer and B cells increased significantly by over 20% following HBOT. The most significant change was noticed in B cells which increased at the 30th session, 60th session and post HBOT by 25.68%±40.42 (p=0.007), 29.39%±23.39 (p=0.0001) and 37.63%±52.73

(p=0.007), respectively.
There was a significant decrease in the number of senescent T helpers by -37.30%±33.04 post-HBOT (P<0.0001). T-cytotoxic senescent cell percentages decreased significantly by -10.96%±12.59 (p=0.0004) post-HBOT. the study indicates that HBOT may induce significant senolytic -effects including significantly increasing telomere length and clearance of senescent cells in the aging populations."

"Aging can be characterized by the progressive loss of physiological integrity, resulting in impaired- functions and susceptibility for diseases and death. This biological -deterioration is considered a major risk factor for cancer, cardiovascular diseases, diabetes and Alzheimer's disease AD among others. At the cellular level, there are two key hallmarks of the aging process: shortening of telomere length and cellular-senescence .
Telomeres are tandem nucleotide repeats located at the end of the chromosomes which maintain genomic stability. Telomeres shorten during replication (mitosis) due to the inherent inability to fully replicate the end part of the lagging DNA strand . Telomere length (TL), measuring between 4 to 15 kilobases, gradually shorten by ~20-40 bases per year and is associated with different diseases, low physica-l performance and cortical thinning of the brain . When TL reaches a critical length, cells cannot replicate and progress to senescence or programmed cell death . Goglin et al. demonstrated that adults with shorter TLs have increased mortality- rates . Shortened TLs can be a direct inherited trait, but several environmental factors have also been associated with shortening TL including stress, lack of physical- endurance activity, excess body mass index, smoking, chronic-inflammation, vitamins deficiency and oxidative stress .Cellular senescence is an arrest of the cell cycle which can be caused by telomere shortening, as well as other aging associated stimuli independent of TL such as non-telomeric DNA damage . The primary purpose of senescence is to prevent propagation of damaged- cells by triggering their elimination via the immune system. The accumulation of senescent -cells with aging reflects either an increase in the generation of these cells and/or a decrease in their clearance, which in turn aggravates the damage and contributes to aging .

A growing body of research has found several pharmacological agents that can reduce the telomere shortening rate . Several lifestyle interventions including endurance training, diets and supplements targeting cell metabolism and oxidative stress have reported relatively small effects (2-5%) on TL3, .
Hyperbaric oxygen therapy (HBOT) utilizes 100% oxygen in an environmental pressure higher than one absolute atmospheres (ATA) to enhance the amount of oxygen dissolved in body's tissues. Repeated intermittent hyperoxic exposures, using certain HBOT protocols, can induce physiological effects which normally occur during hypoxia in a hyperoxic environment, the so called hyperoxic-hypoxic paradox. In addition, it was recently demonstrated that HBOT can induce cognitive- enhancements in healthy aging adults via mechanisms involving regional changes in cerebral blood flow .

On the cellular level, it was demonstrated that HBOT can induce the expression of hypoxia induced factor (HIF), vascular endothelial growth factor (VEGF) and sirtuin (SIRT), stem cell proliferation, mitochondrial biogenesis, angiogenesis and neurogenesis. However, no study to date has examined HBOT's effects on TL and senescent cell accumulation.
The aim of the current study was to evaluate whether HBOT affects TL and senescence-like T-cells population in aging adults." (9)
July 2019
Differences in the Cerebrospinal Fluid of MS Patients May Hold the Key to Therapies That Halt Progression Differences in the Cerebrospinal Fluid of MS Patients May Hold the Key to Therapies That Halt Progression Posted on July 15, 2019 in ASRC News, Featured News, Neuroscience Initiative Advanced Science Research Center at The Graduate Center of the City University of New York "Because the brain is bathed by the cerebrospinal fluid -(CSF), we asked whether treating cultured neurons with the CSF from MS patients with a relapsing/remitting or a progressive disease course would possibly elicit different effects on neuronal mitochondrial function," said the study's primary investigator P. Casaccia, Einstein Professor of Biology at The Graduate Center and founding director of the Neuroscience Initiative at the ASRC. "We detected dramatic differences in the shape of the neuronal -mitochondria and their ability to produce energy. Only exposure to the CSF from progressive MS patients caused neuronal-mitochondria to fuse and elongate while rendering them unable to produce energy. We therefore searched for potential mechanisms of CSF-induced neurodegeneration with the intent to define therapeutic strategies." (10)

Maureen Wentling et al :

"To investigate potential mechanisms of neuro-degeneration, we conducted a functional screening of mitochondria in neurons exposed to the CSF of multiple sclerosis patients with a relapsing remitting (n = 15) or a progressive (secondary, n = 15 or primary, n = 14) disease course. Live-imaging of CSF-treated neurons, using a fluorescent mitochondrial tracer, identified mitochondrial -elongation as a unique effect induced by the CSF from progressive patients. These morphological changes were associated with decreased activity of mitochondria-l complexes I, III and IV and correlated with axonal damage. The effect of CSF treatment on the morphology of mitochondria was characterized by phosphorylation of serine 637 on the dynamin-related protein DRP1, a post-translational- modification responsible for unopposed mitochondrial fusion in response to low glucose conditions. The effect of neuronal treatment with CSF from progressive patients was heat stable, thereby prompting us to conduct an unbiased exploratory lipidomic study that identified specific ceramide species as differentially abundant in the CSF of progressive patients compared to relapsing remitting multiple sclerosis. Treatment of neurons with medium supplemented with ceramides, induced a time-dependent increase of the transcripts-levels of specific glucose and lactate transporters, which functionally resulted in progressively increased glucose uptake from the medium. Thus ceramide levels in the CSF of patients with progressive multiple -sclerosis not only impaired mitochondrial respiration but also decreased the bioavailability of glucose by increasing its uptake. Importantly the neurotoxic effect of CSF treatment could be rescued by exogenous supplementation with glucose or lactate, presumably to compensate the inefficient

fuel utilization. Together these data suggest a condition of 'virtual hypoglycosis' induced by the CSF of progressive patients in cultured- neurons and suggest a critical temporal window of intervention for the rescue of the metabolic impairment of neuronal bioenergetics underlying neurodegeneration in multiple sclerosis patients. "(11)

Lancet Neurol. 2009 Mar

Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis Bruce D Trapp 1, Peter K Stys

"Multiple sclerosis (MS), an inflammatory demyelinating disease, is a major cause of neurological- disability in young adults in the developed world. Although the progressive neurological disability that most patients with MS eventually experience results from axonal degeneration, little is known about the mechanisms of axonal injury in MS. Accumulating evidence suggests that the increased energy demand of impulse conduction along excitable demyelinated- axons and reduced axonal ATP production induce a chronic state of virtual hypoxia in chronically demyelinated axons. In response to such a state, key alterations that contribute to chronic necrosis of axons might include mitochondrial dysfunction (due to defective oxidative-phosphorylation or nitric oxide production), Na+ influx through voltage-gated Na+ channels and axonal AMPA receptors, release of toxic Ca2+ from the axoplasmic reticulum, overactivation of ionotropic and metabotropic axonal glutamate receptors, and activation of voltage-gated Ca2+ channels, ultimately leading to excessive stimulation of Ca2+-dependent degradative pathways. The development of neuro-protective therapies that target these mechanisms might constitute effective adjuncts to currently used immune- modifying agents." (12)

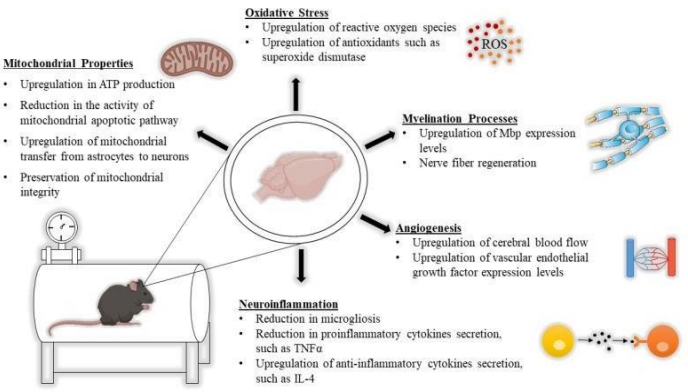


Figure. n 8: Key molecular changes in the brain following hyperbaric- oxygen therapy (HBOT). Mitochondrial properties, oxidative stress, myelination processes, angiogenesis, and neuroinflammation are all altered following HBOT.

"in animal -models, several studies have investigated HBOT's influence on myelin basic protein (Mbp) and remyelination. Baratz-Goldstein et al. studied these effects in a mouse model of mild TBI, applying either immediate or delayed HBOT treatment. They found that both treatments ameliorated the reduced Mbp expression and demyelination compared to the untreated control-group, and that both the treated groups and the sham group had the same measured amount of Mbp expression . Differences between the treated groups and the control- group were already observed 10 days after the beginning of the treatment, meaning that HBOT led to a rather fast recovery, even when limiting the length of the treatment to 4 days. In Kraitsy et al.'s work , HBOT resulted in up-regulation of the expression levels of two specific isoforms of Mbp which are important to myelin structure, upregulation of proteolipid protein (Plp), and increased re-myelination processes."(13)

MR Imaging in Acute Multiple Sclerosis: Ringlike Appearance in Plaques Suggesting the Presence of Paramagnetic Free Radicals

T. Powell et al

"MR studies in three patients with multiple- sclerosis MS have shown clearly defined rings within plaques of demyelination, having signal characteristics consistent with the presence of paramagnetic -material. It is suggested that these appearances represent the presence of free- radicals in the macrophage layer forming the margin of an acute plaque" (14)

MINI-SYMPOSIUM: Recent Advances In Neuroimaging In Multiple Sclerosis, And Their Neuropathlogical Significance

Iron related changes in MS lesions and their validity to characterize MS lesion types and dynamics with Ultra-high field magnetic resonance imaging

Simon Hametner Assunta Dal Bianco Siegfried Trattnig Hans Lassmann First published: 18 July 2018 BRAIN PATHOLOGY

"Iron accumulates with age in the normal human- brain. This process is altered at several levels in the brain of multiple-sclerosis (MS) patients. Since iron is mainly stored in oligodendrocytes and myelin in the normal brain, its liberation in de-myelinating lesions may amplify tissue damage in demyelinating lesions and its uptake in macrophages and microglia may help to more precisely define activity stages of the lesions. In addition, glia- cells change their iron import, export and storage properties in MS lesions, which is reflected by alterations in the expression of iron transport- molecules. Changes of iron distribution in the brain can be reliably detected by MRI, particularly upon application of Ultra-high magnetic field (7 Tesla). Iron-sensitive MRI allows to more accurately distinguish the lesions in MS from those in other inflammatory brain-diseases, to visualize a subset of slowly expanding lesions in the progressive stage of MS and to increase the sensitivity for lesion detection in the gray- matter, such as the cerebral- cortex or deep gray matter nuclei."(15)

"Reactive oxygen- species (ROS) are generated spontaneously in all organisms and cause oxidative damage to biomolecules when present in excess. Accumulated oxidative damage accelerates aging; enhanced antioxidant capacity may be a positive factor for longevity. Recently, numerous studies of aging and longevity have been performed using short-lived animals, however, longevity mechanisms remain unknown. Here we show that a termite Reticulitermes speratus that is thought to be long-lived eusocial insect than other solitary insects uses large quantities of uric acid as an antioxidant against ROS. We demonstrated that the accumulation of uric acid considerably increases the free radical-scavenging activity and resistance against ultraviolet-induced oxidative stress in laboratory-maintained termites. In addition, we found that externally administered uric acid aided termite survival under highly- oxidative conditions.

The present data demonstrates that in addition to nutritional and

metabolic roles, uric acid is an essential antioxidant for survival and contributes significantly to longevity. Uric acid also plays important roles in primates but causes gout when present in excess in humans. Further longevity studies of long-lived organisms may provide important breakthroughs with human- health applications." (16)

Tyrosine Kinase Inhibitor Shows Positive Results in Slowing Slide to MS Disability September 13, 2020

Allison Inserro

Conferences | ECTRIMS: European Committee for Research and Treatment in Multiple Sclerosis

The drug, mastinib, reduced the chance of a confirmed disability progression by 37% in phase 2b/3 study results.

"A selective tyrosine kinase TK - inhibitor being studied for primary progressive multiple sclerosis (PPMS) and nonactive secondary progressive MS showed a 37% reduction in the risk of progression to disability at its lower dose, according to phase 2b/3 study results released Sunday at MSVirtual 2020: 8th Joint ACTRIMS-ECTRIMS Meeting.

The higher dose of the drug was not different than placebo, however, and will not be pursued further.

Mastinib is also being studied in amyotrophic lateral sclerosis, Alzheimer disease, and other indications; it is believed to have neuroprotective effect through its activity on mast cells. It is already approved as a veterinary drug for use in dogs with mast cell cancers.

The study, conducted in 7 countries, compared the efficacy and safety of masitinib at 4.5 mg/kg/day versus matched placebo, or masitinib at 4.5 mg/kg/day with a dose escalation to 6 mg/kg/day after 3 months of treatment versus matched- placebo (ie, the 2 doses were assessed with their own control group).

The primary- outcome measure was the Expanded Disability Status Scale (EDSS) after 96 weeks of treatment in the overall study group as well as in the subgroup analysis. Patients, aged 18 to 75, were randomized (2:1) in the double-blind trial. EDSS changes were assessed at 8 time points between weeks 12 and weeks 96.

During the presentation, the lead- investigator, P Vermersch, MD, PhD, of Hôp. Salengro in Lille, France, noted that 50% of the patients receiving oral mastinib at the lower dose had EDSS scores of 6; the median EDSS score was 5.5, and the mean and median age was about 50. Of the 4.5mg/kg/d group,199 received mastinib and 101 received placebo.

According to the Kaplan-Meier analysis, the cumulative-probability of a confirmed EDSS progression at 12 weeks was reduced by 37% (HR, 0.63; 95% CI, 0.33-1.20; P = .159).

There was also a significant reduced relative- risk of 42% to first progression (HR, 0.58; 95% CI, 0.35- 0.96, P = .034).

The safety analysis showed that 94.5% of patients receiving mastinib had at least 1 adverse event (AE) compared with 87.1% for placebo. Serious AEs were 21.1% for mastinib and 12.9% for placebo, which is in- line with the known safety profile of mastinib, according to the presentation.

Vermersch P, Hermine O. Masitinib in primary progressive (PPMS) and non-active secondary progressive (nSPMS) multiple sclerosis: Results from phase 3 study AB07002. Presented at MSVirtual 2020: 8th Joint ACTRIMS-ECTRIMS Meeting; September 11-13, 2020. Presentation FC04.01." (17)

Prog Neuropsychopharmacol Biol Psychiatry . 2011

Curcumin enhances neuronal survival in N-methyl-d-aspartic acid toxicity by inducing RANTES expression in astrocytes via PI-3K and MAPK signaling pathways

Muh-Shi Lin 1, Kuo-Sheng Hung, Wen-Ta Chiu, Yu-Yo Sun, Shin-Han Tsai, Jia-Wei Lin, Yi-Hsuan Lee

"Methods: Pregnant- female Sprague-Dawley (SD) rats were used for primary culture of cortical neurons, and neonatal 0- to 2-day-old SD rats were used for primary culture of astrocytes. Cultured astrocytes were conditioned with curcumin to prepare astrocyte-conditioned medium (ACM). Real-time polymerase chain reaction was performed to assess RANTES and iNOS mRNA expression in astrocytes following curcumin treatment. ELISA was used to detect astrocyte-secreted RANTES protein in ACM with curcumin treatment. JAK/STAT, PI-3K, PKC and MAPK-inhibitors were used to ascertain whether the effects of curcumin involved these signaling pathways. To evaluate the effects of curcumin-enhanced astrocytes on neuronal survival, cultured cortical neurons treated or untreated with NMDA were incubated in ACM with or without curcumin treatment. Long-term culture (15days in vitro, DIV) was performed to investigate the effects of curcumin-treated astrocytes on the survival of cultured cortical-neurons. Neuronal survival rate was assessed by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction activity assay (for cell viability), and the lactate dehydrogenase (LDH) release assay (for cell death).

We demonstrated that curcumin enhanced RANTES- expression in primary cultured astrocytes, and that this effect was related to activation of PI-3K and MAPK signaling pathways. We found that curcumin inhibited iNOS expression in primary cultured astrocytes in non-stressed condition. We also found that neurons exposed to NMDA and cultured with curcumin treated ACM, which characteristically exhibited elevated RANTES -expression showed higher level of cell viability and lower level of cell death. Using a small interfering RNA (siRNA) knockdown model, we found evidence that the basal- level of RANTES expression in non-stimulated astrocytes provided neuroprotection.

We postulate that the enhanced neuronal survival by curcumin treatment in NMDA toxicity and long-term cultures was in part attributable to elevated astrocyte-derived RANTES expression via activation of PI3K/MAPK signaling pathways. (18)

Nalini Mistry et al :

"Glyoxal, a reactive aldehyde, is a decomposition product of lipid hydroperoxides, oxidative deoxyribose breakdown, or autoxidation of sugars, such as glucose. It readily forms DNA-adducts, generating potential carcinogens such as glyoxalated deoxycytidine (gdC). A major drawback in assessing gdC

formation in cellular DNA has been methodologic sensitivity. We have developed an mAb that specifically recognizes gdC. Balb/c mice were immunized with DNA, oxidatively modified by UVC/hydrogen peroxide in the presence of endogenous metal-ions. Although UVC is not normally considered an oxidizing agent, a UVC/hydrogen peroxide combination may lead to glyoxalated bases arising from hydroxyl radical damage to deoxyribose. This damaging system was used to induce numerous oxidative -lesions including glyoxal DNA modifications, from which resulted a number of clones. Clone F3/9/H2/G5 showed increased reactivity toward glyoxal-modified DNA greater than that of the immunizing antigen " (19)

According research article 2019 The Turing Machine Theory for Some Spinal Cord and Brain Condition, A Toxicological – Antidotic Depurative Approach:

"in some neuro-degenerative or inflammatory brain or spinal cord disease a process that can
Depurate Form some toxic metabolites or immune-products can delay the progression of some severe disease.
Is possible to introduce the hypotesis that a pharmacological, antidotic, or medical devices or other physic strategy can help in this setting . (20)

Possible Mechanism of action must be evaluated. Immnunological links: mabs monoclonal antibodies Differential solubility properties (idrophilic- lipophilic balance) Molecular weight (differential)
Dimension – diameter of particles size Differential in electrical charge Chemical: Complexant agent, chelant Enzymatic-remove

acilitator of excretions: chemical groups to be linked to increase the clearance
Increase factor that improve catabolism or clearance of toxic substantia
Free radicals blockers strategy (LOCAL MICROENVIRONMENT) Flogosys control (sustained local action) " (20)

Experimental Project Hypotesys

In order to verify the efficacy and safety of a SPINAL CORD neuro tissue (or LCR) dialitic like - or brain depurative procedure is possible to Hypotize a in vitro model (animal model ?) whit a spine cord or brain tissue to be submitted to the procedure , using different kind of solution or other strategies (lime MD) to depurate form toxic substanties responsible of progression of some neuro-degenerative disease .

Immnunological links:mabs, towards flogotic factors, TK inibithors Differential solubility (idrophilic- lipophilic balance), Molecular weight (differential), Dimension – diameter of particles, Differential in electrical charge .
Chemical: complexant agent, Enzymatic – remove ,Facilitator of excretions : chemical groups to be linked to increase clearance Increase factor that improve catabolism or clearance of toxic substantia, Free radicals blockers strategy scavengers . Flogosys control (sustained local action). In
Vitro animal Model.

Clearance of the system (brain waste flux) status:

Kinetics Transport at the neuro-vascular unit across the glial barrier and BBB: depends on the solubility, molecular weight and diameter of the protein and if a pharmacological or a non-pharmacological system (MD or other physic process) can provide better results.
The affinity of innovative pharmacological molecule must be evaluate to choose the 1 with high link with the toxic substantia (FREE oxygen radicals, Iron), with the best profile for an efficacy tissue clearance.

Other parameter must be take in consideration like: lipophilic-idrophilic profile of toxic substantia, molecular weight, molecular conformation, links profile, electrical charge, hydrogen binds, and other useful to have an efficacy extraction. Safety of the procedure must be evaluate (histology, electric conduction and other possible) for the evaluation of The efficacy of a local free radicals blockers system or other chemical physical system able to contain the unbalances in oxygen and glucose utilization and related free radical production after an immune stimuli.

2 sample :

A) sample containing animal neurons in vitro , added with CSF of MS affected
B) sample containing neurons in vitro added with CSF of MS affected plus DETOXICANT MEDIUM
The detoxicant medium : can be a free radical local system or a medical devices that use a chemico physical method to control free radical production
Time of exposition :7-30 days
After this time all the sample must be analized using laboratory test to verify toxicity. Number of sample : 5 sample for A and 5 for B
Statistical data : CHI square test $p < 0,05$

Discussion

Related literature reported it is possible to verify that:
"significant underutilization of oxygen in MS raise important questions regarding mitochondrial respiratory dysfunction and neurodegeneration of the disease".
"Recent data indicate that mitochondrial injury and subsequent energy failure are key factors in the induction of demyelination and neurodegeneration"
"The interconnected mechanisms responsible for free radical production in patients with multiple sclerosis are as follows: (i) inflammation-induced production of free radicals by activated immune cells, (ii) liberation of iron from the myelin sheets during demyelination, and (iii) mitochondrial injury and thus energy failure- related free radical production. "
"Treatment of neurons with medium supplemented with ceramides, induced a time-dependent increase of the transcripts levels of specific glucose and lactate transporters, which functionally resulted in progressively increased glucose uptake from the medium. Thus ceramide levels in the CSF of patients with progressive multiple- sclerosis MS not only impaired mitochondrial respiration but also decreased the bioavailability of glucose by increasing its uptake. Importantly the neurotoxic effect of CSF treatment could be rescued by exogenous supplementation with glucose or lactate, presumably to compensate the inefficient

fuel utilization. Together these data suggest a condition of 'virtual hypoglycosis' induced by the CSF of progressive patients in cultured -neurons and suggest a critical temporal window of intervention for the rescue of the metabolic impairment of neuronal bioenergetics underlying neuro-degeneration in multiple sclerosis patients."

"Can we consider waste of immune -systems some accumulation substantial in some brain Pathology?"

Conclusion

In order to search new pharmacological – toxicological strategy for MS it is interesting to verify the efficacy of a Detoxicant procedure .

The umbalances of immune system with activation of immune cells , related free radicals production Demyelination and mitochondrial injury can be considered as and endogen toxicological movens.

If considered this aspect relevant can be a detoxicant strategy but not only using a local blockers system of free radical but also a medical devices that can produce the same effect whit a physical way.

Scavengers or chelants or other physical strategy :but it must be efficacy and of persistence effect and in the local microenvironment without tissue neuronal toxicity .

The key factor is a local action , long time of exposition but with great attention to preserve neurons life.

IN ordinary way in some poisoning are used antidothes also to depurate brain form heavy metals so it is not a new approach. (Mercurious derivates and chelant agents .)

Also in the case of mercurios derivates anche chelat agents use it is relevant the irdatation of patient to avoid other organ toxicity (renal) .

So antidothic use but according safe rules to preserve other tissue form toxicity in elimination phases. The same it is crucial to find strategy to block free radical production t in local place preserving the Tissue involved.

Can we think to a dialytic -like process in next years for neuro-inflammatory disease ?

Clarification: this article is produced without any diagnostic or therapeutic intent , only to submit To the researcher an hypotesys of work

Conflict of Interests : no

Ethical Consideration : all ethical consideration must to be respected

References

1. Spitsin S., Koprowski H. Role of uric acid in multiple sclerosis (неопр.) // Curr. Top. Microbiol. Immunol.. — 2008. — Т. 318. — С. 325—342. PMID 18219824. (англ.).
2. Marrie RA. Environmental risk factors in multiple sclerosis aetiology (англ.) // The Lancet : journal. —Elsevier, December 2004. — Vol. 3, no. 12. — P. 709—718. — PMID 15556803. (англ.)
3. Compston A., Coles A. Multiple sclerosis. (англ.) // The Lancet. — Elsevier, October 2008. — Vol. 372, no. 9648. — P. 1502—1517. — PMID 18970977. (англ.).
4. Hernán M.A., Jick S.S., Olek M.J., Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. (англ.) // Neurology (англ.)русск. : journal. — Wolters Kluwer (англ.)русск., 2004. — September (vol. 63, no. 5). — P. 838— 842. — PMID 15832457. (англ.).
5. 5.World Health Organization Global Advisory Committee on Vaccine Safety: Response to the paper by
6. MA Hernán and others in Neurology 14th September 2004 issue entitled «Recombinant Hepatitis B Vaccine and the Risk of Multiple Sclerosis» (англ.). 6.M. Munzel. Multiple Sclerosis: The Psychosomatic Consequence of Unsuccessful Bonding (англ.). —Karger Publishers, 2002. — P. 35—48.
7. Characterizing Brain Oxygen Metabolism in Patients with Multiple Sclerosis with T2-Relaxation-Under- Spin-Tagging MRI Yulin Ge, Zhongwei Zhang, Hanzhang Lu, Lin Tang, Hina Jaggi, Joseph Herbert, James S Babb, Henry Rusinek, Robert I Grossman First Published January 18, 2012 Other Find in PubMed J Cereb Blood Flow Metab. 2012 Mar; 32(3): 403–412.
8. Oxid Med Cell Longev. 2015; 2015: 725370. Inflammation, Iron, Energy Failure, and Oxidative Stress in the Pathogenesis of Multiple Sclerosis Published online 2015 May 27. Lukas Haider * Department of Neuroimmunology, Center for Brain Research and Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria
9. AGING Research Paper Volume 12, Issue 22 pp 22445—22456 Hyperbaric oxygen therapy increases telomere length and decreases immunosenescence in isolated blood cells: a prospective trial
10. Yafit Hachmo1, * , Amir Hadanny2,3,4, * , Ramzia Abu Hamed1 , Malka Daniel-Kotovsky2 , Merav Catalogna2 , Gregory Fishlev2 , Erez Lang2 , Nir Polak2 , Keren Doenyas2 , Mony Friedman2 , Yonatan Zemel2 , Yair Bechor2 , Shai Efrati1,2,3,5 July 2019 Differences in the Cerebrospinal Fluid of MS Patients May Hold the Key to Therapies That Halt Progression Differences in the Cerebrospinal Fluid of MS Patients May Hold the Key to Therapies That Halt Progression posted on July 15, 2019 in ASRC News, Featured News, Neuroscience Initiative Advanced Science Research Center at The Graduate Center of the City University of New York September 2019 A metabolic perspective on CSF-mediated neurodegeneration in multiple sclerosis
11. Maureen Wentling, Carlos Lopez-Gomez, Hye-Jin Park, Mario Amatruda, Achilles Ntranos, James Aramini, Maria Petracca, Tom Rusielewicz, Emily Chen, Vladimir Tolstikov ... Show more Brain, Volume 142, Issue 9, September 2019, Pages 2756–2774,
12. Lancet Neurol 2009 Mar;8(3):280-91. doi: 10.1016/S1474-4422(09)70043-2. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis Bruce D Trapp 1, Peter K Stys

13. Molecular and Therapeutic Aspects of Hyperbaric Oxygen Therapy in Neurological Conditions Inbar Fischer and Boaz Barak Biomolecules 2020 MR Imaging in Acute Multiple Sclerosis: Ringlike Appearance in Plaques Suggesting the Presence of Paramagnetic Free Radicals
14. T. Powell,1 3 J . G. Sussman,2 and G. A . B. Davies-Jones2 AJNR 13:1544- 1546. Nov/ Dec 1992 0 195-6 108/ 92/ 1306-1544 © A merican Society of Neuroradiology
15. MINI-SYMPOSIUM: RECENT ADVANCES IN NEUROIMAGING IN MULTIPLE SCLEROSIS, AND THEIR NEUROPATHLOGICAL SIGNIFICANCE Open Access Iron related changes in MS lesions and their validity to characterize MS lesion types and dynamics with Ultra-high field magnetic resonance imaging Simon Hametner Assunta Dal Bianco Siegfried Trattnig Hans Lassmann First published: 18 July 2018 BRAIN PATHOLOGY
16. Uric acid, an important antioxidant contributing to survival in termites Eisuke Tasaki,Hiroki Sakurai,Masaru Nitao,Kenji Matsuura,Yoshihito Iuchi Published: June 13, 2017
17. Tyrosine Kinase Inhibitor Shows Positive Results in Slowing Slide to MS Disability September 13, 2020 Allison Inserro Conferences | ECTRIMS: European Committee for Research and Treatment in Multiple Sclerosis
18. Prog Neuropsychopharmacol Biol Psychiatry . 2011 Curcumin enhances neuronal survival in N-methyl-d-aspartic acid toxicity by inducing RANTES expression in astrocytes via PI-3K and MAPK signaling pathways
19. Muh-Shi Lin 1, Kuo-Sheng Hung, Wen-Ta Chiu, Yu-Yo Sun, Shin-Han Tsai, Jia-Wei Lin, Yi-Hsuan Lee Published: 01 February 2003 Novel Monoclonal Antibody Recognition of Oxidative DNA Damage Adduct, Deoxycytidine-Glyoxal Nalini Mistry, Ian Podmore, Marcus Cooke, Paul Butler, Helen Griffiths, Karl Herbert & Joseph Lunec Laboratory Investigation volume 83, pages241–250(2003)
20. luisetto M (2019) The Turing Machine Theory for Some Spinal Cord and Brain Condition, A Toxicological – Antidotic Depurative Approach J Neurol Neuro Toxicol Volume 3(1): 2019 1