Three Causal Factors of ALS Disease Outbreak and a Primer for Healing – A Theory and Case Study[a]

Contents

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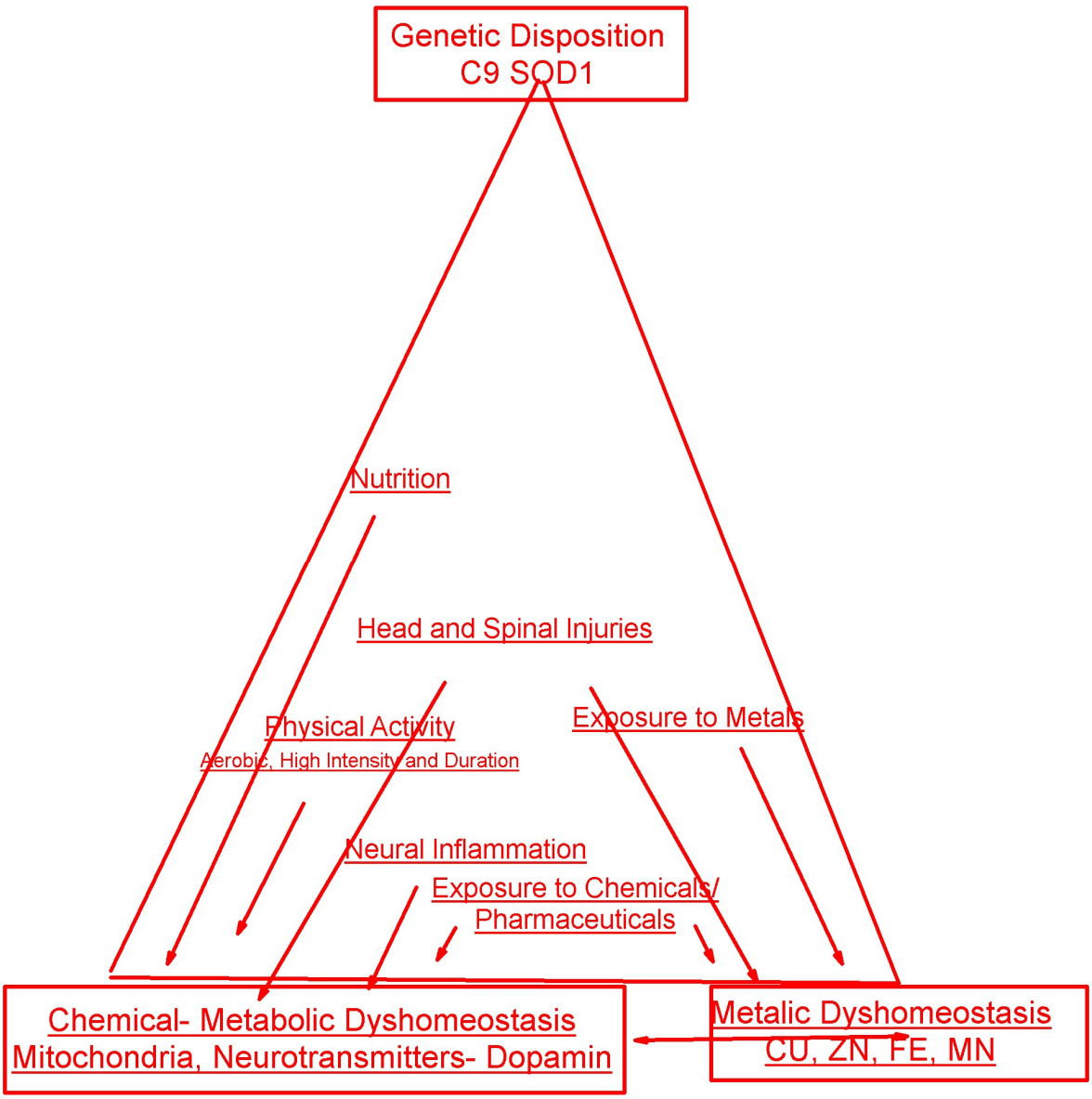
Preface

I met Yulia many years ago and we remained friends on Facebook. Recently, we chatted and I found out that she has been sick with ALS since the sickly and troubled year of 2020. During the month of the outbreak of her disease, March 2020, I wrote an article about a treatment using colloidal copper against viral (respiratory) diseases.[1] Three and a half years later, we are trying to precipitate the cure for ALS, among other things, thru metal homeostasis.



Hypothesis

Two Environmental Factors and One Genetic Disposition

The disease with the mutation that Yulia has [C9] typically begins at a relatively young age,[2] with relatively rapid deterioration, and mental decline (in 50% of patients).[3] This did not happen in Yulia's case. This may support the claim that environmental factors (exposure to chemicals &drugs) are more dominant than the genetic aspect.

Yulia Gonik-Kolesik, 37 years old, married and the mother of two children, resident of Netanya, Israel. Yulia suffered from severe anxiety disorders [Generalized anxiety disorder (GAD)] and additional psychological issues for many years. In 2019, Yulia experienced a severe anxiety attack that lasted six months. In the last month of the attack, March 2020, she was hospitalized in a psychiatric ward, and towards the end of the hospitalization, symptoms of neural degeneration began to appear.

Yulia has the mutation in the C9 gene, associated with ALS. In other words, she had the genetic susceptibility that could lead to the disease. It's possible that the environmental factors that triggered the disease were the very stressful period of hospitalization, during which she received very strong psychiatric medications with severe side effects related to the nervous system. This situation may have caused damage to the body's metabolism (and liver), and simultaneously, led to an imbalance (dyshomeostasis) of metal transport and metal levels in the body (especially in the brain and spinal cord). The combination of disrupted metal balance and impaired metabolism led to neurological damage, and over time, caused the body to fail in repairing the damage and returning to balance.

The first medication Yulia received during hospitalization: Risperidone[4] – is known to damage the liver,[5] and therefore can affect copper levels in the body and copper absorption etc. But she only took this medication for a few days.

The second medication Yulia received is "Seroquel" by AstraZeneca. Yulia continued to take this medication after being discharged from the hospital, and in total, she took the medication at a high dosage for about six months.

There is a causal link between psychiatric disorders and the onset of ALS.[6] The use of certain medications significantly increase the risk of the onset of ALS.[7] Quetiapine - the active ingredient in Seroquel, binds to neurotransmitter receptors in the brain, including dopamine, which plays a role in motor control. There are certain motor disorders

[extrapyramidal symptoms] that scientists believe are related to the inhibition of the neurotransmitter dopamine in the brain.

A common side effect of Seroquel is depression of the central nervous system.[8] In a study on mice, the substance had a depressing effect on their movement (in mice with dopamine deficiency: increased activity in the brain area - median raphe nucleus, and exaggerated-abnormal movement).[9] According to Yulia: "It causes speech and walking problems. And that's how it started for me. And I was sure it was side effects. I'm sure that's what started my degeneration".

Yulia took Seroquel for six months at a high dosage. Although she stopped taking Seroquel, it is possible that the signaling of damage within the cells continued- a phenomenon in which cells continue to respond to danger even after it has passed, and begin to act independently of the organism – similar to what happens in cancer. The ongoing cellular response causes inflammation and damage to the function of metabolism and the cells' power stations - the mitochondria.

A 2013 study shows that a higher level of inflammation amongst ALS patients is associated with a shorter survival time.[10] A study published in October 2022 strengthens the theory that the disease is related to metabolic disorders. Its conclusions are that even within the framework of a more aggressive ALS disease (related to the C9 gene mutation), patients survived longer if they also had a thyroid disorder (that is related to metabolism).[11]

The immediate proximity between hospitalization and disease onset suggests a causal link. Assuming there is a causal link, it can be supposed that psychiatric medications caused some imbalance or damage. The damage may be related to the imbalance (dyshomeostasis) of metals in the body, and to (damage) imbalance of cellular metabolism.

In addition, Yulia suffered a spinal injury in her youth (as a result of weightlifting), which caused a severe disc herniation. Yulia says that she suffered greatly from this injury and was often paralyzed by pain and had to lie on her back even in public places.

We can see that the statistics of high-risk groups for ALS are athletes, especially in contact sports such as American football, where there is a lot of trauma to the spine and brain.[12] Traumatic spinal injuries cause inflammatory processes in the area of injury (and in the nerves in the area), which can cause neurological damage and deterioration.[13] A study published in 2014 concludes that it is likely that pathological changes related to ALS occur following neuroinflammation of sensory nerves in the spine [DRG, CNG].[14] In addition, traumatic head and spinal injuries can cause a metal imbalance in the body.[15]

Populations by occupations and their health implications in relation to the 2 main factors of the disease

The statistics in the USA regarding population groups suffering from ALS can strengthen the hypothesis about the two main environmental factors leading to the onset of the disease - disruption of metabolic balance and disruption of metal balance in the body.[16]

Occupational Risk Factors

Construction and Metal Workers

A study on a population in the New England area in the USA, between 1993 and 1996, showed that construction workers (but not managers) had a 2.9 times higher risk of developing ALS, and metal workers had a 3.5 times higher risk of developing the disease. Additionally, the study found that exposure to paint thinners, various oils, cooling fluids, dry cleaning materials, and other substances leads to a higher risk of developing the disease.

Risk Factors:

- Exposure to lubricating, cooling, and cutting oils showed a particularly high risk of developing the disease.

- Exposure to certain materials (Aliphatic chlorinated hydrocarbons, ethylene/propylene glycols, glycol ethers, heptane hexane) showed an increased risk of developing the disease, especially among non-smokers.[17]

Military Veterans

According to another study, the largest group with ALS in the USA is male veterans, with twice the chance of developing ALS compared to men who were not in the military. It's important to note that there is no mandatory service in the US, and only about 0.5% of Americans serve in the military (0.75% if including the National Guard and reservists).

Risk Factors:

- ALS is almost the only disease occurring more frequently among veterans, regardless of the historical period in which they served.[18]

- Soldiers undergo strenuous training and active service, making them particularly vulnerable to extreme changes in metabolism.

- Due to the use of ammunition and various types of military equipment, soldiers are exposed to metals.[19]

Firefighters

A 2010 study examining about 73,000 death certificates from 24 states in the USA found that firefighters had twice the risk of developing ALS.[20] Researchers linked this to physical exertion and the phenomenon of oxygen deficiency (hypoxia).

Risk Factors:

- Intense and prolonged aerobic physical activity

- Exposure to toxins and metals through fire smoke, firefighting equipment, etc.[21]

Athletes

A 2019 study among Italian professional soccer players found that the risk of soccer players developing ALS is about twice that of the general population.[22]

Another study from the same year on contact sports found two areas that increase the risk of developing ALS:

1. Professional sports

2. Sports where athletes tend to suffer repeated concussions (especially severe concussions) and blows to the cervical spine.[23]

Risk Factors:

- Clear criterion of intense and prolonged aerobic physical activity and/or trauma to the spine and head (leading to neuroinflammation).

- The criterion of exposure to toxins or metals is unclear (although soccer fields are sprayed with various chemicals).

- An additional sub-factor of trauma to the brain and (cervical) spine is present.

Interestingly, athletes who experience the most trauma to the spine, such as wrestlers, and trauma to the brain, such as boxers, are not included in the statistics of increased risk for ALS (at least in these studies). Despite the fact that boxers do tend to develop other neurological diseases, such as Parkinson's disease (a disease related to the

neurotransmitter dopamine) and dementia. These two diseases are characterized by pathology that is primarily cerebral and less related to the spinal cord. From this, it may be possible to conclude that inflammation and damage to nerve cells due to head injuries alone do not tend to lead to ALS. On the other hand, it is possible that the reason for this discrepancy is that players on a soccer field are exposed to substances that boxers in the ring are not exposed to.

Farmers

Farmers are often exposed to various toxins.[b] [24] [25]A comparative study from 2014, which reviewed 1,720 articles (of which 22 were ultimately included in the analysis), attempted to examine the prevalence and risk of ALS among people working in agriculture. The study found the following:

Risk Factors:

- 44% increased risk of developing the disease among people exposed to pesticides.

- 42% increased risk for people working in agricultural professions.

- In an analysis of case-control studies, exposure to pesticides among men increased the risk of developing the disease by 96%.

- When using professional judgment to estimate the degree of exposure in these case-control studies, the risk of developing the disease increased to 204%.[26]

[b] One of the most dangerous substances is the natural toxin Ricin, which is found in Castor Beans. Study show that Ricin causes damage and death of motor neurons.

Conclusion

These studies highlight the two main criteria contributing to metal and chemical-metabolic imbalance:

1. Prolonged and strenuous physical activity (aerobic).

2. Exposure to chemicals or metals.

The development of chemical – metabolic imbalance in organs [Liver] and cellular organelles [Mitochondria, UPS Proteins] as a factor in the onset of ALS[27]

Studies show a connection between metabolic disorders and the onset of ALS. Other studies demonstrate the link between mitochondrial dysfunction and neurodegenerative diseases (including ALS). Additionally, there are studies indicating that liver damage is significantly more common among ALS patients.

Nutrition has a significant impact on the chemical-metabolic balance and on the onset and development of the disease. Yulia reports that she always ate everything with a lot of salt, much more salt than normal (although her diet was otherwise considered healthy - salads, low calories, etc.). Studies show that mutations in sodium channel genes can cause disruptions in these channels, thereby creating dysregulation in sodium transport to cells, which is necessary for transmitting electrical signals between nerves. As a result, or due to changes in muscle excitability, neurotoxicity (damage to nerve cells-excitotoxicity) occurs.[28]

This is just another possible sub-factor in the onset of the disease. It is unknown whether Yulia has these mutations in sodium channels that cause these disorders, but there is a study showing that a high-salt diet (without the genetic component) can cause neurological

damage. The study found that a high-salt diet reduces the flexibility of nerves associated with morning anticipation (return to waking activity after sleep) and therefore may cause disturbances in sleep-wake cycles (insomnia). Furthermore, the study found that excess salt in the diet causes a significant reduction in the levels, secretion, and transmission of neurotransmitters in the brain and suppresses the processes of axon production (which enable communication between nerves), thereby causing significant neurological disturbances associated with neurological diseases such as Parkinson's and Alzheimer's.[29]

Immune system Dyshomeostasis and neuroinflammation

There is evidence that development of immune system imbalance plays a role in the progression of the disease. Studies indicate that genetic factors, such as mutations in certain genes [SETX], need to be present in both the nervous system and the immune system in order to cause motor disorders (in mice), and that dysfunctional immune system activity characterizes a specific type of the disease [ALS4].[30] Various studies show that microglial cells, the immune cells of the brain and spinal cord, are activated in the disease and cause inflammation in the central nervous system, which is characteristic of ALS.[31].

There is evidence of an autoimmune response against nerve cells in the disease, through the infiltration of immune cells [T-cells] into the central nervous system. Additionally, studies show that the composition of gut bacteria (microbiota) in ALS patients can affect the immune system and thereby contribute (among other factors) to the development of the disease.

Another study shows that initially, the immune system's response to nerve damage is positive [anti-inflammatory] and protects nerve cells, but at some point, after chronic stimulation, the immune system's response shifts to a stage that promotes inflammation [pro-inflammatory] and neurotoxicity [neuroinflammation and neurotoxicity], exacerbating the severity of the disease. According to the study, in some cases,

hyperactivation of the immune system, specifically of microglia or astrocytes, can precede nerve damage, indicating excessive inflammation as a primary pathogenic factor in ALS.

On the other hand, in other cases, an insufficient immune response to damage [Immunodeficiency], or poor clearance of molecules released by damaged nerve cells [DAMPs], can lead to the accumulation of proteins and other molecules, resulting in chronic inflammation and nerve cell death. Therefore, it is important to properly assess the dosage and duration of immune system-related drugs in order to achieve a balance between suppressing harmful excessive inflammation and maintaining an immune response essential for damage repair and protection[32].

Dyshomeostasis of Gut Microbiota

There is evidence suggesting that the 'community of microorganisms' - the gut microbiota - has a causal link to neurological diseases, and specifically to Alzheimer's disease. The gut microbiota system produces neurotransmitters and other molecules that can influence brain function, and there are reciprocal bidirectional interactions between the brain and the gut microbiota.

A study published in October 2023 shows that transferring gut microbiota from Alzheimer's patients to healthy mice is sufficient to induce Alzheimer's-like symptoms in the mice. The microbiota transplantation led to a significant reduction in the formation of neural tissues in the Dentate Gyrus (DG) area of the hippocampus in the brain, indicating that the microbiota negatively affects the production and survival of new neurons in this brain region. Moreover, the microbiota caused a significant reduction in the length and complexity of dendrites in cells with a specific protein called Doublecortin (DCX), which is associated with neuron production.

The research demonstrated that the gut microbiota and intestinal structure of Alzheimer's patients differ from those of healthy individuals in the control group. Bacteria of the genus Coprococcus showed a positive correlation with cognitive tests (MMSE scores), while bacteria of the genera Desulfovibrio and Dialister showed a negative-inverse relationship with cognitive test results. The mice exhibited decline in cognitive tasks related to pattern separation, spatial memory, recognition memory, and location identification. These impairments are comparable to the cognitive deficits associated with Alzheimer's disease.[33]

Additionally, the study revealed significantly higher levels of calprotectin protein in feces, indicating intestinal inflammation, among Alzheimer's patients, and showed that the disease is characterized by general inflammation in the body and specifically in the intestines. Finally, the research discovered differences in metabolite profiles between mice with Alzheimer's microbiota and healthy mice in the control group. Many of the metabolites found in mice with Alzheimer's microbiota have previously been proven to be associated with Alzheimer's disease and neurocognitive disorders. A key metabolite of this sort is the amino acid Taurine, which was found in reduced quantities in mice with Alzheimer's microbiota. Taurine is known to help protect cells (including neurons) from oxidative damage, assist in blood sugar regulation by increasing insulin sensitivity, and also help clear toxic substances from the liver, thereby protecting the liver.[34]

Metabolic Dyshomeostasis

Studies show that glucose intolerance, high blood lipid levels, and a shift to fat-based (aerobic) metabolism, along with damaged mitochondria in motor neurons, are common physiological markers among ALS patients.[35] Research indicates that ALS patients suffer from an excessively rapid metabolism accompanied by significant weight loss (and rapid fat loss), and animal studies show that defects related to energy production in the body precede neurological damage in the disease.[36]

Furthermore, a phase 2 clinical trial found that high-calorie diets are safe and well-tolerated by patients, with a significant reduction in disease side effects.[37] A study analyzing the cerebrospinal fluid of ALS patients found high levels of glucose and Alpha-Hydroxybutyrate, which is produced during the digestion of glucose and lactate, and leads to the production of the neurotransmitter Gamma-Hydroxybutyrate (GHB), important for sleep, mood, and appetite. These high levels are an early biological sign of insulin resistance.[38]

Studies show that insulin and glucose tolerance, which are two central characteristics of metabolic syndrome, are associated with ALS.[39] Another study found that type 2 diabetes actually slows the onset and progression of the disease.[40] Additionally, a diabetes medication (Pioglitazone) was found to improve motor function and survival in mice with the $SOD1^{G93A}$ gene mutation.[41] [42] This hints at a possible shortage of available sugar for cells or an inability of the body to use existing sugar for energy needs in the disease.

The excessively rapid metabolism in ALS patients may be related to overexpression of the TDP-43 protein (associated with glucose balance in skeletal muscles) in motor neurons (in ALS, protein accumulation in the brain and spinal cord damages motor neurons). Overexpression of this protein leads to an increase in the amount of the main metabolite pyruvate, related to glucose metabolism.[43] Studies show that a high-calorie, high-fat diet (and a higher amount of body fat)[44] is actually beneficial for survival,[45] and reduces the risk of mortality from the disease.[46]

There are studies showing that to compensate for the rapid breakdown of carbohydrates and sugars (glycolysis) occurring in the body, normal (non-mutated) SOD1 protein increases the supply of amino acids for protein and glutathione synthesis, while mutated SOD1 protein fails in this action, leading to cell toxicity and nerve cell damage.[47] Muscle cells performing glycolysis gradually lose their ability to use glucose and then switch to

lipids (fats) as an alternative energy source, and this metabolic switch occurs mainly in the pre-symptomatic part of the disease.[48]

Studies show that environmental pollution and exposure to toxins lead to cellular-metabolic damage. A study conducted from 2006 to 2013 in the Netherlands found a link between long-term exposure to air pollution and ALS. The study found that exposure to soot, carbon dioxide, and nitrogen oxide ($PM_{2.5}$, NO_2, NOx) is associated with ALS disease onset (though exposure to these substances is not exclusively related to air pollution).

Air pollution can lead (among other things) to the development of ALS, as a result of very small particles of pollutants (Ultrafine airborne particles) crossing the blood-brain barrier. These particles cause chronic inflammation in the brain, oxidative damage, damage to white matter in the brain, and activate microglial cells - immune system cells of the brain and spinal cord that release inflammatory substances.[49]

A meta-analysis shows a suspected link between exposure to pesticides [organochlorine insecticides (OCs), pyrethroids, herbicides, fumigants] and ALS.[50] Another study found a connection between the use of fat and paint solvents and ALS in men. The study found that men exposed to benzene (+20%), methylene chloride (+23%), and Perchloroethylene (+21%) have a higher adjusted chance of developing ALS.[51]

Damage to mitochondrial organelle function

One study shows that the mutated SOD1 gene can cause the production of proteins that fold incorrectly on the surface of mitochondrial organelles. The study emphasizes the importance of mitochondrial function-focused treatments, such as coenzyme Q10 and creatine. The study explains that there is a protein, which is a transcriptional co-activator that plays a crucial role in various biological processes, including mitochondrial function.

The protein Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) plays an important role in preventing neurodegeneration and mitochondrial organelle dysfunction. Studies on mice with a mutation in the SOD1-G93A gene showed that abundant expression of the PGC-1α protein can slow the progression of ALS, improve motor function, and extend the patient's life.[52]

One study showed that the C9 gene is related to energetic and metabolic balance in the body by stabilizing an area in the mitochondria. The protein produced by C9 reaches the inner part of the mitochondria, where it regulates the process by which cells produce energy as food (oxidative phosphorylation - OXPHOS), by regulating TIMMDC1, which is an essential factor for building the first enzyme in the energy production chain (OXPHOS complex I). The research showed that the gene is significantly related to energy balance in the body by stabilizing the mitochondrial complex I assembly process, and that a mutation in the gene can explain part of the development of ALS.[53]

Another study showed that amino acids dipeptide repeats [specifically (GR)80], which are produced by the mutated C9 gene, are associated with mitochondrial ribosomes and lead to mitochondrial dysfunction and increased oxidative damage, which cause damage to the DNA of stem cells that produce motor neurons.[54]

An additional study showed that widespread degeneration in mitochondria found in motor neurons caused mice with a SOD1 mutation to develop ALS.[55] Other studies even show that degeneration of mitochondrial organelles occurs in the pre-symptomatic stage of the disease, before the loss of motor neurons.[56]

An interesting study suggests that the onset of the disease is related to complex relationships between genetic factors, aging, and environmental injuries. The study argues that among people with genetic susceptibility to the disease, impairment of mitochondrial activity is the central factor. Environmental factors that damage mitochondria and cause

the disease include exposure to organophosphates,[c] heavy metals (such as mercury and lead), and strenuous physical activity, while some environmental injuries such as viral infections and exposure to heavy metals can occur at a young age and manifest many years later in ALS.

The mechanism proposed by the researchers is the death of motor neurons, which increases the metabolic stress on other nerve cells, leading to a chain reaction that results in failure. Astrocytes supporting nerve cells can switch to a state of attempting to rescue nerve cells, thereby impairing the ongoing maintenance of nerve cells.[57]

Another study points to the genetic link to mitochondrial problems that lead to the disease. Genes such as FUS, SOD1, and CHCHD10 that have undergone mutations lead to impairment of the mitochondrial energy production process, increased oxidative damage, and calcium dyshomeostasis. Since mitochondria are responsible for balancing calcium levels, impairment of mitochondrial activity can lead to disruption of calcium homeostasis, which exacerbates the disease. Finally, the study suggests possible drugs for treating and improving mitochondrial function, such as antioxidants, mitochondrial membrane regulators, and treatments using embryonic stem cells.[58]

An additional study emphasizes the genetic link to mitochondrial problems that lead to the disease. The research points to evidence that mutations in SOD1, C9ORF72, TARDBP, FUS, VCP, VAPB, OPTN, TBK1, SQSTM1, ALS2, SIGMAR1, CHCHD10, and KIF5A genes lead to impairment of mitochondrial activity. The study suggests various treatments such as gene therapy (CRISPR) and emphasizes the complexity of the disease, with multiple pathological mechanisms leading to impaired mitochondrial activity.[59]

[c] There are studies showing that commercial pilots and flight attendants have a higher incidence of ALS. It is speculated that the recycled air inside aircrafts may contain various substances and oils from the engines and other aircraft mechanisms.

Damage to Liver Function

A study showed that 76% of ALS patients suffered from fatty liver, compared to 19% of people without ALS.[60] Studies show that there is a significant metabolic change among ALS patients, including in liver metabolism.[61] [62]

It's important to remember that the liver is the organ that stores most of the copper in the body and plays a central role in copper metabolism, in transporting copper to the rest of the body [with the help of a protein (ceruloplasmin)], and in excreting copper from the body through the intestine (with the help of bile fluid produced in the gallbladder).

Furthermore, the liver is the main organ responsible for metabolism in the body, including the processing of carbohydrates, fats, proteins, and various substances (including drugs and medications). The liver is responsible for storing and releasing glucose, and part of the pathogenesis of ALS is related to insulin and glucose tolerance, which are two central characteristics of metabolic syndrome. This is linked to peri-neural (the area surrounding nerve cells) and muscle cell processes, but it is also known that liver damage can lead to insulin resistance,[63] and high blood sugar levels.[64]

It is very likely that the symptoms of metabolic syndrome, which exist among ALS patients, are related to impaired liver function (perhaps, among other things, as a result of prolonged exposure to various substances, such as medications, as happened to Julia). Moreover, research shows that people suffering from non-alcoholic fatty liver syndrome, which is a metabolic disorder, are three times more likely to suffer from a personality disorder.[65] [66] This also relates to metabolic disorders that affect the brain.

Example of Metabolic Dyshomeostasis that leads to neurodegeneration and ALS

Consumption of Strong Medications ⇒ Damage to Liver Function ⇒ Development of Metabolic Syndrome ⇒ Cells Gradually Transition to an Overactive Metabolism Using

Fat (Not Sugars) ⇒ Nerve Mitochondria Lose the Ability to Supply Sufficient Energy to Nerve Cells ⇒ Neurodegeneration and ALS

Damage to the Ubiquitin –Proteasome System [UPS]

The ubiquitin-proteasome system (UPS) is responsible for protein degradation (ubiquitin is a small protein that attaches to other proteins, thereby "giving instructions" and modifying them, while the proteasome acts as an enzyme - receiving the instruction and breaking down the proteins). Damage or imbalance (dyshomeostasis) in this system leads to protein misfolding and accumulation in nerve cells. Moreover, the UPS is involved in regulating and maintaining synaptic activities of nerve cells and in the process of axon degradation.[67]

When this system becomes imbalanced, the mechanism that breaks down and destroys proteins is impaired (and therefore also related to the regulation of sugar and fatty acid metabolism), a condition that is also linked to certain types of cancer (because the body doesn't destroy cancer cells and they continue to multiply). Studies show a connection between impaired UPS activity and the development of ALS.[68] [69]

There are studies showing that protein aggregates (associated with ALS) in motor neurons contain ubiquitin, and the accumulation of proteins isolates and suppresses ubiquitin, thereby reducing the amount of ubiquitin within cells. This leads to damage to the UPS and the ability to remove these proteins - thus worsening the condition.[70] This pathological process has also been observed in patients with the SOD1 mutation, where protein degradation (breakdown) occurs without ubiquitin or ATP. Additionally, impaired metal binding to SOD1 due to mutations leads to metal-free SOD1 proteins that function as a substrate for the proteasome - Proteasome 20S, resulting in the breakdown and destruction (and degeneration) of many nerve cells.[71] On the other hand, there is a study showing that certain types of copper [NC-CuCl and NC-CuCl2] cause inhibition of the UPS, potentially leading to cancerous growths.[72]

A study showed that UPS impairment is not observed in the pre-symptomatic stages of ALS disease, suggesting that this impairment is not the primary mechanism causing motor neuron degeneration, but rather a factor that contributes to the deterioration of the disease over time.[73] Apparently, the process of protein accumulation and damage to the protein degradation system (the UPS) is bidirectional, and it is unclear what causes what[20;74] sometimes it's "the chicken" and sometimes "the egg".[75]

A new study from the Technion University in Israel, shows that destabilization in this system (change in ubiquitin instruction signs) leads to the accumulation of toxic proteins, which exhibit Alzheimer's disease pathology. The researchers have engineered an RNA molecule that silences one of the system's components and hope to develop a drug in this way.[76] [77] Another study shows that ALS patients have reduced expression of UPS genes and consequently reduced ubiquitin, which can lead to defects in nerve cells and their death.[78]

Proteasome imbalance can cause accumulation of misfolded and damaged proteins in motor neurons, which can lead to cell death.[79] The activity of a certain type of proteasome [Calpains] is increased in ALS,[80] causing degradation of cytoskeletal proteins like spectrin and neurofilaments, which can impair axonal transport and contribute to motor neuron dysfunction.[81] Another type of proteasome [Caspase-3] associated with cell death (apoptosis) is linked to neurodegenerative diseases such as ALS.[82] The activity of this enzyme (proteasome) in ALS increases in motor neurons, which can lead to the death of these cells.[83] Studies indicate a link between mutations in certain ALS-related genes and disruption of proteasome activity, leading to accumulation of misfolded proteins and impaired cellular function.[84]

Cyclophilin proteins play a role in various cellular activities, including protein folding. Cyclophilin A can slow down the protein degradation process by binding to and inhibiting proteasomes.[85] This inhibition can cause various diseases,[86] thus there is a therapeutic

direction of using cyclophilin protein inhibitors for cancer and ALS.[87] In a study on the use of cyclophilin inhibitors for ALS treatment, researchers found that extracellular Cyclophilin A is present in larger quantities in the brain and spinal cord of mice with ALS. Additionally, the researchers found that by using a specific Cyclophilin A inhibitor, they could reduce neuroinflammation and extend the lifespan of ALS-affected mice.[88]

Another mechanism for protein degradation is autophagy, which envelops proteins in a type of bubble [autophagosome] that breaks them down. This mechanism can work in conjunction with the UPS, for example, ubiquitin marks proteins, which are then degraded by autophagy. When the autophagy mechanism is disrupted, cellular dyshomeostasis occurs, leading to the accumulation of toxic proteins. Studies show that genetic therapy [Beclin 1 gene therapy] can be used to enhance the autophagy process, thereby protecting against neurodegeneration.[89] However, treatment by intervening in the autophagy mechanism is complex, and the outcome varies depending on the type of disease (and according to the internal classification - such as ALS associated with SOD1 mutation versus other types).[90]

Furthermore, there are proteins called Heat Shock Proteins that protect cells from stress damage caused by heat, infection, or injury. These proteins are considered beneficial and protective of motor neurons in neurodegenerative diseases. However, in some cases of neurodegenerative diseases, overexpression of these proteins can promote the formation of toxic protein aggregates, because these stress-protective proteins can stabilize misfolded proteins, thereby prolonging their harmful effects.[91] [d] [92]

[d] Regarding heat and stress protection, it is worth mentioning a study that showed that cold therapy (intermittent mild hyperthermia of the entire body) is beneficial to ALS-affected mice.

Factors Leading to Dyshomeostasis of the UPS in ALS disease

A 2009 study showed that proteotoxic stress, which is trigged, amongst other things, by the accumulation of misfolded proteins (TDP-43 and others), can damage the UPS system, thus becoming a factor that promotes the development of neurodegenerative diseases.[93] [94]

Another study indicates that the proteasome is one of the molecular targets of organo-metallic compounds (containing tin metal bound to carbon atoms) called organotins. The binding of these toxic compounds (or direct binding of tin atoms) to the cellular proteasome leads to proteasome inhibition, protein accumulation, and cell death.[95] These toxic compounds are used in various industrial applications, agricultural use (pesticides and fungicides), and as stabilizers in plastic products. In other words, exposure to environmental toxins (including thru the use of plastic products) may cause damage or suppression of the UPS system and lead to protein accumulation and cell death.

An additional study shows that the use of pesticides (common in China) [paraquat, rotenone, chlorpyrifos, pendimethalin, endosulfan, fenpyroximate, tebufenpyrad] causes mitochondrial damage and proteasome suppression, and this may be a potential mechanism of neurodegeneration in Parkinson's disease.[96]

As we saw in a previous chapter, metabolic imbalance related to glucose breakdown and excessive tolerance to sugar and insulin is associated with the onset of ALS. Interestingly, there are studies showing that when certain cells are exposed to (chronic) excess of sugar, this leads to a 20-25% reduction in proteasome activity and results in cell death [Caspase-3-dependent apoptosis]. This demonstrates a link between high sugar levels and damage to proteasome activity.[97] A 2019 study emphasizes that substances formed when sugars are activated in response to proteins or fats [advanced glycation end products (AGEs)] accumulate in the body over time and interfere with UPS function, potentially leading to various types of chronic diseases, including neurological disorders.[98] This is particularly

interesting in the context of sugar and insulin tolerance, similar to metabolic syndrome, existing in ALS patients.

A study found a significant link between impaired UPS activity and impaired immune system activity, neurodevelopmental disorders such as autism, attention disorders, speech disorders, and motor disorders. Additionally, the study found a possible link between uncontrolled inflammation and the pathogenesis of psychiatric disorders, including neurodevelopmental disorders. However, most patients with these disorders do not experience symptoms common in chronic inflammation. This can be explained by the fact that the inflammation is only regional and not systemic, especially in the central nervous system, which develops inflammation in response to UPS damage.[99]

Research shows that a mutation in the gene [UBQLN2] associated with ALS and dementia leads to failure in proteasome binding, resulting in the accumulation of proteasome substrates. Furthermore, studies point to the connection between the cellular system responsible for protein production and transport [Endoplasmic Reticulum-ER], with mitochondrial activity responsible for calcium homeostasis and redox regulation. When the activity of mitochondria and/or the protein regulation system [ER] is impaired, it can lead to ER stress and activation of the UPS. If the system suffers from certain mutations, this activation may fail. The research also emphasizes the importance of autophagy and the impairment of autophagic processes causing disease onset.[100]

As we have seen in a previous chapter, liver activity is related to metal balance and metabolic balance, and therefore, disruption of liver activity is associated with the onset of ALS. A 2021 study indicates that ubiquitin plays a role in the pathogenesis of chronic liver disease. Moreover, higher levels of proteasomes are associated with the severity of liver cancer [hepatocellular carcinoma]. Metabolic changes in the liver (such as in fatty liver) can impair UPS activity. Additionally, oxidative damage and inflammation are indicators

of UPS system damage, as well as indicators of liver damage. The study indicates that a state of UPS impairment is common among people with liver damage.[101]

This raises the question - what comes first? Or what is the arrow of causality - the chicken or the egg... Does UPS damage lead to liver damage, or (more logically in my opinion), liver damage (metabolic damage) leads to UPS damage, which leads to deterioration in ALS disease.

Possible treatments for restoring balance to the system

Research shows that ALS patients are at a lower risk of developing cancer (20% less than the general population), especially lung cancer (77% less), but at a higher risk for site-specific cancers such as testicular (382%) and salivary gland (527%). The study found that in general, ALS has relative protection against the risk of developing cancer, and this is similar to the results of studies in other neurological diseases such as Alzheimer's and Parkinson's.[102] [e]

Proteasome inhibitors, such as [Carfilzomib, Oprozomib, Ixazomib, Brotezomib] show effectiveness in fighting cancer. These drugs can cause an imbalance in the process of protein breakdown and exchange, causing cancer cells to die.[103] On the other hand, proteasome supporters such as valproic acid,[104] and resveratrol,[105] have shown effectiveness against ALS in animal studies. Additionally, there are studies showing the effectiveness of using small molecules that promote proteasome activity as a treatment for neurodegenerative diseases.[106] A different study suggests various autophagy (and proteasome) promoting treatments [Pyrazolone, Fluphenazine, Berberine, etc.] as a treatment for metabolic imbalance related to proteins and the UPS system in ALS disease.[107]

[e] A bit of dark humor for ALS patients – look at the bright side! ALS protects you from cancer. Focus on the positive.

Metal Dyshomeostasis (especially copper and iron) as a factor in ALS onset

Copper is essential for mitochondrial activity, and the mitochondria itself is responsible for copper homeostasis in the body.[108] [109] There are studies showing the central role of copper homeostasis in relation to brain diseases,[110] neurodegeneration,[111] and the relationship of copper levels and other metals such as zinc and selenium in neurodegenerative diseases.[112] Copper plays an important role in nerve conductivity,[113] synaptic function, axonal targeting in the nervous system, and synaptogenesis.[114] Studies also show imbalances of other metals, such as magnesium, aluminum, and calcium, in the spinal cord of ALS patients.[115] [116] [117] A study using innovative X-ray technology found that people with ALS have higher levels of metals such as chlorine [Cl], potassium [K], calcium [Ca], zinc [Zn], and bromine [Br] in their nerve cells.[118] On the other hand, a different (observational) study found a link between lower levels of selenium [Se] and zinc [Zn] and ALS.[119]

A study published in 2020 examined past metal balance of ALS patients' youth, using special tests on patients' teeth. The study found that metal levels during the childhood of ALS patients (long before they were diagnosed with the disease) were much higher than in control groups (49% more chromium at age 15, 82% more manganese, 65% more nickel, and almost 2.5 times - 146% - more tin at age two, and zinc at age 6).[120]

There is a study showing that a reduction in calcium availability in cells, caused by impaired mitochondrial activity leading to calcium dyshomeostasis in the intercellular space, causes extensive protein [TDP-43] splitting by the death of zymogens (proenzymes), resulting in protein accumulation in motor neurons, which is associated with ALS.[121] Another study shows that an increase in calcium levels in the cytoplasm of cells due to

impaired mitochondrial activity leads to stress in the endoplasmic reticulum, associated with neuroinflammation and leading to insulin resistance.[122]

Another study explains that neuronal damage caused by imbalance in intercellular calcium and overactivation of glutamate receptors (which serves as a neurological transmitter of glial cells) is caused by impaired activity of brain glial cells [astroglial cells] leading to disruption of synaptic activity of nerves and neurodegenerative diseases such as ALS.[123] [f] These studies suggest that there may be a link between metal imbalance, leading to impaired mitochondrial activity of satellite glial cells, to consistent release of glutamate from these cells, and to sensory neuron depolarization, thereby leading to neurological symptoms and nerve damage [especially of lower motor neurons (LMN's)].[124] [g] Glutamate and its receptors are implicated as having a significant causal link to ALS. In another study indicates that motor neuron excitotoxicity is mediated mainly through the areas of glutamate receptors [AMPR] in the central nervous system.[125]

Imbalance in other metals,[126] [127] such as iron, has also been linked to neurological diseases,[128] such as ALS.[129] Very high levels of iron (and in some cases including high levels of zinc) were found in the spinal cords of ALS patients,[130] and in the brains of patients with ALS and Parkinson's-dementia.[131] [132]

[f] The study suggest performing cell replacement (a transfusion) of astrocytes, microglia, and T-lymphocytes as a procedure for treating the disease [ALS].

[g] "These data make it appear likely that in ALS the chronic mitochondrial dysfunction in satellite glial cells resulting from an imbalance of metals leads to hyperactivation of sensory neurons, which in turn causes persistent depolarization and consequent degeneration of LMNs through activation of spinal cord and brain stem AMPA receptors."

Table 2
Imbalance of metals in ALS patients.

Region	Cu	Zn	Fe	Mn	Reference
Blood	↓	→		↑	Kapaki et al. (1997)
	↑	↓		→	Peters et al. (2016)
	↑	↑		↑	Roos et al. (2013)
	→	→	→		De Benedetti et al. (2015)
CSF	↑	↑	↑	→	Hozumi et al. (2011)
	↓	→			Kapaki et al. (1997)
	↑	↑		↑	Roos et al. (2012), 2013
Spinal cord		↑	↑		Markesbery et al. (1995)
		↑	↑		Tomik et al. (2006)
			↑		Ince et al. (1994)
			↑		Kasarskis et al. (1995)
				→	Kihira et al. (1990)
				↑	Miyata et al. (1983)
				↑	Mitchell et al. (1991)
Brain (motor cortex)			↑		Kwan et al. (2012)
		↓	↑		Yasui et al. (1993)

↑, increase; ↓, decrease; →, no change.

From the research of Nakagawa and Shizuo (yellow highlight – added by me)[133]

Studies show that the accumulation of iron in oligodendrocytes [134] [135] (and also in astrocytes),[136] damages the myelin layer that protects neural axons, thereby disrupting the communication of electrical signals between neurons, leading to oxidative damage that can harm the myelin layers and these cells and, and results in reduced energy supply to motor neurons and to their degeneration.[137] [138] Oligodendrocytes are involved in the construction, maintenance, and repair of motor neurons, and damage to them harms motor neurons. It is worth noting that copper is necessary for the process of myelination of nerve cells.

* In Yulia's blood tests, there is a deficiency of transferrin but normal iron levels. Transferrin is the substance that transports iron to oligodendrocytes (and astrocytes). Are these cells suffering from iron imbalance? An area in the brain responsible for motor control [Basal ganglia] is known to have a high percentage of iron. Is there a causal link between these facts?

A study (on mice) demonstrated that receiving copper supplements resolves pathological problems related to excess iron in the body.[139] Iron absorption is related to copper

absorption, as the two metals "compete" for absorption in the digestive system (as well as zinc), so an imbalance of one affects other metals.

Cadmium is a metal proven to be dangerous to humans. People are exposed to cadmium in industrial areas, from prolonged exposure to air pollution, from smoking and from industrial foods such as rice, corn and flour. There are studies showing the damage cadmium causes to neurons.[140] [141] Studies have found high amounts of cadmium in the blood and nervous system of ALS patients.[142] [143] High amounts of the metal were found in the liver and kidneys of patients.[144] Another study, in a battery manufacturing plant, showed that ALS disease among plant workers was caused by cadmium toxicity by reduction of SOD1 activity.[145]

One study showed that transferring zinc to SOD1 mutations improved motor abilities and survival of mice. The treatment did not increase zinc levels in SOD1 or the spinal cord but did increase overall copper levels and SOD1 copper content, so the authors of the study concluded that the medical effect of this zinc treatment may actually result from the release of copper ions as a result of the zinc transfer. The results support the theory that copper deficiency in SOD1 may contribute to ALS pathology.[146]

In contrast to the approach of adding copper, there are studies showing that removal of copper slows disease progression and improves survival, and there is a study showing that among younger people with ALS there is a higher than normal concentration of copper.[147] Copper accumulation can lead to oxidative stress and oxidative damage to nerve cells. One way to prevent copper accumulation in the brain is to use Copper Transporters Inhibitors. Another way is through genetic treatments that correct mutated genes or transfer new genes. These methods have shown success in animal studies.

Several studies tested the use of a certain type of copper-containing molecule [CuATSM] to transport copper to mitochondrial cells damaged in ALS patients. Initial results of some

of them showed that the substance slows disease progression and improves survival chances.[148]

An example of the importance of balancing copper levels in the body can be found in Alzheimer's disease. A meta-analysis found a copper deficiency in the brains of Alzheimer's patients.[149] There is theory that a reduction in bioavailable copper in the body is related to disturbances in iron metabolism, which is known to be associated with neuronal degeneration.[150] On the other hand, Parkinson's patients were found to have excess copper in the brain (400mM compared to 70mM in a healthy brain).[151] An effective treatment for this is the use of a synthetic, water-soluble peptide (a substance composed of 2 or more amino acids) that can remove copper from natural peptides [Amyloid-β peptides] that accumulate in the brain in Alzheimer's disease.[152]

Back to the 'pro copper' side, another study showed a decrease in copper and an increase in iron levels in a brain area [Substantia Nigra], where neuronal death occurs in Parkinson's disease.[153] It is possible that part of copper's protective action on nerve cells stems from balancing iron absorption in the body (since both metals compete for absorption in the intestines). In Parkinson's disease too, there are studies showing the connection of low copper levels with the disease. It is demonstrated that using molecules capable of transferring copper to the brain can slow the disease. A similar treatment has been proven as a possible therapeutic strategy for ALS, using a copper-containing molecule - diacetylbis(N(4)-methylthiosemicarbazonato) copper(II) =(CuII-ATSM).[154] [155]

There are studies showing that copper homeostasis has a statistically significant link to neurological diseases. There are different forms of copper chelation from the body and different forms of adding bioavailable copper to the body. Some studies show that excess copper is harmful and some that copper deficiency is. The mechanisms of copper processing and transport in the body are complex, so it is not always simple to understand the causal order of things.[156]

As we can see, both excess copper and copper deficiency can cause neurological diseases, such as Parkinson's disease. Therefore, we should strive for copper balance (homeostasis), not excess or deficiency.

A 2020 study shows that metallic imbalance in the body, including that of zinc, iron and manganese [Mn], can lead to the spread of prion proteins and lead to impaired synaptic activity and neuronal death. Manganese and iron "compete" for absorption in the body, similar to the "competition" between copper and zinc, so an abnormal increase in one of them leads to a decrease in the opposing metal and to metallic imbalance in the body.[157] [158]

According to another study by Nakagawa and Shizu, Metallic imbalance can affect the balance of cerebrospinal fluid and can be a significant factor in the formation and development of neurodegenerative diseases. The study mentions that neuroinflammation is also a factor in the formation of these diseases, but metallic imbalance may be a more significant factor, leading to cell death. The study also suggests a possible link between metallic imbalance and psychiatric conditions such as mood disorders and schizophrenia.[159]

A study published in 2013 shows that exposure to environmental toxins, such as pesticides, agricultural materials, as well as smoking, intense physical activity and electromagnetic fields, increases the risk of developing ALS. Additionally, the study shows that exposure to heavy metals such as mercury and lead (which people are exposed to, among other things, by smoking), increase the risk and intensity of the disease. Electrical workers such as electricians and power plant workers may be at higher risk of developing the disease due to exposure to heavy metals and electromagnetic fields. Excessive exposure to selenium, which is found in excessive amounts in drinking water in certain areas, increases the risk of developing ALS. Finally, abnormal levels of copper and zinc in the body and their changes in SOD1 enzymes are related to the pathology of the disease.[160]

Additional Examples of Metabolic Dyshomeostasis that leads to neurodegeneration and ALS

‖: Consumption of Strong Medications ⇒ Damage to Liver Function ⇒ Copper Dyshomeostasis ⇒ Iron Dyshomeostasis ⇒ Iron Accumulation and Neurodegeneration ⇒ ALS :‖

‖: Metal Exposure ⇒ Metal Dyshomeostasis ⇒ Motor Neurons Do Not Receive Enough Copper ⇒ Neurodegeneration and ALS :‖

‖: Spinal Injury ⇒ Neural Damage and Inflammation ⇒ Disruption of Metal Transport Process & Dyshomeostasis ⇒ Neurodegeneration and ALS :‖

Example of Metabolic Dyshomeostasis in Conjunction with Chemical-Metabolic Dyshomeostasis that leads to neurodegeneration and ALS

‖: Spinal Injury ⇒ Metal Dyshomeostasis ⇒ Neurodegeneration ⇒ Damage to Liver Function ⇒ Damage to Metabolism and Inability to Repair the Damage Sustained as a Result of the Metal Dyshomeostasis ⇒ Neurodegeneration & ALS :‖

Genetic Factors

מוטציות בגנים האחראים על ייצור והובלת חלבונים קשורות לתהליך התפתחות המחלה. המוטציות מובילות לקיפול לא נכון של חלבונים ולהצטברות שלהם באזור של תאי העצב, שהוא תהליך עיקרי אשר מוביל למחלה.

Mutations in the genes responsible for protein production and transport are related to the disease development process. These mutations lead to protein misfolding and their aggregation in parts of nerve cells, which is a major process that leads to the disease.

The Mutation in the C9orf72 gene

The mutation in C9orf72 is associated with a critical stage in protein production [Phenylalanine-tRNA aminoacylation],[161] and additionally, studies show that C9 directly interacts with the protein related to copper transport to cells [CTR1]. This interaction may interfere with the protein's ability to transport copper to cells, leading to copper imbalance in the body and accumulation of toxic proteins and copper in the brain, resulting in neurological damage.

Yulia has a history of anxiety and mental health issues, which can be attributed to her difficult childhood. Furthermore, Frontotemporal Dementia is associated with psychiatric problems, physiological issues, and problems with the C9 gene. There is a tendency for misdiagnosis of psychiatric problems when the actual cause may be dementia. This type of dementia can manifest in motor problems similar to ALS. This raises the question: Is it possible that Julia is actually suffering from this type of dementia or rather, an imbalance in this part of the brain, which are also related to her other problems and symptoms?

The damage or alteration in the C9 gene is not sufficient to recreate the onset of the disease, and multiple factors acting together are necessary. An example of such a chain of

factors could be cell death [Excitotoxicity] due to overstimulation of receptors for a neurotransmitter called glutamate, which is essential for normal brain function.[162]

The SOD1 gene mutation and metal (copper) homeostasis

In the context of the mutation in SOD1, there is research whose conclusions show that increasing the metallic content of this protein's enzyme can be beneficial in ALS disease caused by the mutation in the [SOD1] gene, which encodes the enzyme.[163] Copper deficiency has been linked in studies to ALS caused by mutation of the SOD1 gene, and it has even been shown that the degree of copper deficiency in the mutated SOD gene is proportional to the clinical severity level of ALS.[164] Furthermore, studies show that because astrocytes express SOD1, they are sensitive to imbalances in copper and zinc levels.[165]

There is another theory- that a copper deficiency in an area of the brain also related to anxiety and panic - the Locus coeruleus, and in another area, the Substantia nigra, is associated with a reduction of copper in the SOD1 enzyme. This causes an accumulation of lipid and cholesterol -carrying proteins (Apolipoproteins) and thereby inhibits the ability to protect neurons from oxidative damage.

On the other hand, there are studies showing that copper removal helps against the disease. One study shows positive results of copper removal using Clioquinol, which improves the condition of multiple sclerosis patients.[166] Another study (on mice) shows that a substance that helps remove copper [Ammonium tetrathiomolybdate – TTM] from the spinal cord, which accumulated as a result of mutated SOD1 genes, delays the onset of the disease, its progression, and prolongs survival.

However, copper removal has direct and indirect effects even unrelated to changing copper levels in the body. Removal of copper ions from SOD1 causes a significant reduction in the activity of these genes and a decrease in their accumulation, and

contributes to the construction of such genes without metal, which break down easily and therefore reduce the toxic effects of these genes.[167] Furthermore, copper-removing substances affect the homeostasis of other metals in the body. Therefore, the results of copper removal experiments can be interpreted in such a way that reducing the overall amount of copper in the body is not the factor that improved the patients' condition.[168]

The genetic factor does not cause the disease by itself – most people with the ALS related mutations will not get the disease

A 2023 analysis showed a penetrance[h] of C9orf72 for ALS of less than 25% using two different methods. This means that potentially 75% or more of people with this mutation may not develop ALS.[169] Another study found the maximum population penetrance for either ALS or frontotemporal dementia to be 33% for C9orf72 (95% CI: 20.9% to 53.2%). This suggests that up to 67% of C9orf72 mutation carriers might not develop these conditions.[170]

The same study also provided penetrance estimates for other major ALS-associated genes (It's important to note that penetrance can be age-dependent, meaning the risk may increase with age):

- SOD1: 54% penetrance (95% CI: 32.7% to 88.6%). Suggesting potentially 46% or more people carrying the gene mutation may not develop the disease.

- TARDBP: 38% penetrance (95% CI: 21.1% to 69.8%). Suggesting potentially 62% or more people carrying the gene mutation may not develop the disease.

[h] Penetrance = the rate of occurrence of a trait controlled by a specific gene is observed in people carrying that gene - in other words, the probability that a trait resulting from a specific gene will be expressed.

- FUS: 19% penetrance (95% CI: 13.0% to 28.4%). Suggesting potentially 81% or more people carrying the gene mutation may not develop the disease.

These findings indicate that a considerable number of people carrying ALS-associated genetic mutations may never develop the disease. In other words, the genetic factor most likely has to coincide with environmental factor/s for the onset of the disease to occur. Overall, these findings strengthen my hypothesis regarding the three causal factors, where at least two of which are required for the onset of the disease.

Examples of Processes based on Genetic Factors that lead to neurodegeneration and ALS

Ⅱ: C9 Gene Mutation ⇒ Metal Dyshomeostasis ⇒ Accumulation of copper and toxic proteins in the brain ⇒ Neurodegeneration and ALS :Ⅱ

Ⅱ: SOD1 Gene Mutation ⇒ Copper Deficiency in SOD1 Genes/Enzymes ⇒ Copper Deficiency in Certain Areas of the Brain ⇒ Protein Aggregation and Oxidative Damage ⇒ Neurodegeneration and ALS :Ⅱ

Example of a Process of Copper Dyshomeostasis in Conjunction with Chemical-Metabolic Dyshomeostasis and Genetic Proclivity that Lead to Neurodegeneration and ALS

‖: Spinal Injury ⇒ Inflammation and Neurodegeneration | Consuming Potent Medication ⇒ Liver and Metabolic Stress and Damage ⇒ Metal Dyshomeostasis | Body Fails to Correct Imbalance Due to C9 Mutation ⇒ Neurodegeneration and ALS :‖

Medical data related to Yulia's diagnosis

There are many causal factors here. It's important to try to understand and distinguish between cause and effect, and what preceded what ('the chicken or the egg').

Blood tests

5.09.2023:

Blood copper: 86 mcg/dl - slightly low, on the border of normal values with a minimum of 65 mcg/dl.

Compared to a previous blood test (before illness) on 28.07.2019: This test was not performed.

Iron [Fe]: Normal level of 100 micg/dl

Compared to previous blood test (before illness) on 28.07.2019: Iron: 127 micg/dl

However, the iron carrier -

Transferrin: ⇩ Low - 242 mg/dl, where the lower limit is 250 mg/dl.

Compared to a previous blood test (before illness) on 28.07.2019: This test was not performed.

Indication of liver and/or metabolism (and mitochondria) problems:

Bilirubin: ⬇ Low - 0.2 mg/dl, where the lower limit is defined as 0.3 mg/dl.

Compared to a previous blood test (before illness) on 28.07.2019: Bilirubin (U) - Negative

ALT (GPT): ⬆ High - 32 U/I, where the upper limit is defined as 31.

Compared to a previous blood test (before illness) on 28.07.2019: Normal - 13 U/I

Additionally:

Creatinine: ⬇ Low - 0.25 mg/dl, where the lower limit is defined as 0.5 mg/dl.

Compared to a previous blood test (before illness) on 28.07.2019: Slightly above lower limit - 0.53 mg/dl

Protein Total: ⬇ Low protein level 6.3 g/dl, where the lower limit is defined as 6.6 g/dl.

Compared to a previous blood test (before illness) on 28.07.2019: Normal (on the low border) - 7 g/dl

Sodium: On the lower limit: 136 mmol/l, where the range is from 136-146.

Compared to a previous blood test (before illness) on 28.07.2019: Normal - 140 mmol/l.

Hope for Healing

When a patient is diagnosed with ALS, it is necessary to perform several essential tests (apart from genetic tests) to understand the specific expression of the disease in the patient. An MRI examination of the brain and spine to detect metal levels is crucial - [see Appendix B: Types of MRI tests for metal levels in the brain and spine].

Additionally, it is advisable to conduct a cerebrospinal fluid test for levels of specific proteins [[NfL, pNfH] related to nerve cells [tau], responsible for metabolic transport to cells, and the protein [TDP-43], associated with RNA transport and regulation of genetic

expression. Regarding this protein, it is necessary to check if nerve cell aggregates contain the aforementioned protein which includes the UPS protein marker [Ubiquitin] that displays to the cell system which proteins need to be broken down.[171] Comprehensive blood and urine tests are also essential, with emphasis on metabolic factors and inflammatory factors (which are released into the blood when nerve cells are damaged), such as [NfL, pNfH].

Additionally, it is worthwhile to examine the patient's history regarding diet, physical activity, and injuries to the spine and brain. A questionnaire like this one should be presented: [172]

Before you were diagnosed with the disease, what was your lifestyle like:

1. Did you regularly consume large amounts of alcohol?

2. Did you regularly use prescription drugs that can cause severe side effects/damage?

3. Did your diet include a lot of salt?

4. Did your diet include a lot of sugar?

5. Did you smoke heavily (cigarettes)?

6. Was your diet very rich in carbohydrates?

7. Was your diet very rich in fat?

8. Did you engage in intense and prolonged sports activities for extended periods?

9. Did you suffer from serious head or spinal injuries?

10. Do you think you may have been exposed to dangerous substances or metals?

After receiving the data, it is possible to build a map of the patient's personal metal and metabolic dyshomeostasis. Apart from the genetic factor, the focus should be on two roads to recovery: metal balance and chemical-metabolic balance.

Treatments for Metal Homeostasis (with emphasis on copper)

In March 2020, I wrote an article about using colloidal copper as a treatment against viruses and various medical conditions. There are different technologies and types of copper for treating copper deficiency, but the treatment I propose is unique (and unconventional) and may have unique advantages of copper absorption with nanoparticles, and copper absorption through the respiratory system.[173] It should be noted that there are studies showing that treatments with gold nanoparticles significantly improve the condition of ALS patients (69% reduction in mortality risk in a follow-up about two and a half years after the start of the trial).[174] [175]

There are various ways and different types of metals for treating different conditions of metal dishomeostasis in the body, specifically in the nervous system, brain, and spinal cord.[176] CuII(atsm), for example, has been proven as a potential effective treatment for delivering copper to the central nervous system,[177] [178] and Cu II(gtsm) has shown neuroprotective properties in animal studies on Parkinson's disease.[179] There is a type of molecule [Ionophore] that can transfer ions into cells. Such molecules are used in combination with copper [Copper Ionophores] [such as ATSM, GTSM, 8-hydroxyquinoline, peptide complexes] to add copper to cells and increase intracellular copper levels if they are low. Additionally, this molecule's transfer technology can be used to treat cancer.[180]

Studies show that the use of certain peptides, such as [D-Peptide] of the [RD2RD2] type, have demonstrated therapeutic efficacy in ALS mice (with the Sod1 genetic component), in reducing neuronal inflammation and slowing disease progression.[181] Other studies show that the use of copper peptides such as [CuATSM] in ALS mice, protects and improves neuronal function, reduces inflammation, and slows disease progression.[182]

There is a phenomenon where excess copper causes cell death [Cuproptosis]. Copper binds to certain proteins [lipoylated proteins in the tricarboxylic acid (TCA) cycle], causing protein accumulation and imbalance of iron-sulfur cluster proteins, leading to cell distress due to misfolding and protein accumulation [Proteotoxic Stress], and to cell death. However, the toxicity and damage caused by excess copper to cells is likely also related to mitochondrial dysfunction, leading to increased production of reactive oxygen species (ROS) and suppression of key enzymes.[183]

Chelating-removing excess copper from the body can prevent the aforementioned cellular damage. In vitro studies have shown that removing copper from beta-amyloid peptides (A β) can prevent their accumulation, allow enzymes to break down these peptides, reduce oxidative damage, and protect against cell death.[184]

Copper mixtures as a therapeutic agent can also lead back to copper homeostasis in the brain, thereby protecting against neurodegeneration. In other diseases, such as skin diseases and coronary artery disease, the positive effect of these mixtures can be explained as a result of encouraging SOD activity, which relieves oxidative stress. A study showed that treatment with copper sulfate in mice with artificial diabetes [STZ-diabetes] led to a reduction in blood glucose levels and improvement in pancreatic morphology.[185] This finding links the balance of metals in the body, especially copper, with chemical-metabolic balance.

There are copper compounds created in order to reduce inflammation caused by reduced SOD activity. The compound [NSAID-Cu] reduces inflammation, apparently due to its

action mimicking SOD activity.[186] On the other hand, copper-chelating substances such as [Tetrathiomolybdate (TM)] have shown effectiveness in reducing inflammation.[187]

In other cases, copper chelators such as [Dp109, ammonium tetrathiomolybdate(TTM), N-acetylcysteine] have shown improved survival in ALS mice.[188] [189] Furthermore, iron-chelating treatments, such as with Deferiprone, [190] and other substances, have been proven effective in reducing damage to motor neurons and extending survival in ALS mice. [191]

However, one of the problems with using metal chelators is that they can bind uncontrollably to ions of metals necessary for the body. Moreover, many chelators are made of large molecules [Hydrophilic Molecules], which cannot cross the blood-brain barrier and reach the brain, and this impairs their ability to treat neurodegeneration and other brain pathologies by removing metals. There is an ammonia-absorbing mineral [Nano-Zeolite] marketed under the name TRS, which can remove heavy metals from various areas of the body, but there is still not enough clinical information about it and there are some concerns about side effects.[192] [193]

The article by White and Duncan provides a comprehensive review of various copper compounds and their use for treating various pathologies.[194]

Treatments for Chemical-Metabolic Homeostasis [Organs & Organelles]

In the process of restoring chemical-metabolic balance, we need to reduce inflammation and oxidative stress in relevant areas of the body (liver, brain, spine), improve cellular activity, focusing on organelles and structures related to metabolism (such as mitochondria), and improve (and heal) the central organs related to metabolism (such as the liver).

Research shows that administering melatonin to mice with a mutation in the SOD1 gene inhibits clinical symptoms, reduces neurodegeneration, and prolongs survival.[195] Additional substances - [Oxaloacetate, Dexpramipexole], which act on mitochondria and other systems, have shown potential for treating ALS,[196] [197] as presented in the research by Nakagawa and Shizuo.[198]

Studies show a positive therapeutic effect in inhibiting glutamine release and glutamine receptors, such as with the drug Riluzole,[199] which increases survival time in the final stage of the disease, and Perampanel, which inhibits glutamate receptors in the central nervous system [AMPA Receptors].[200]

However, we are looking for a complete cure. This is only one aspect of the treatment, and there is a need to "attack" from at least two main directions (including metal balance). Blocking distress receptors (proteins) that cause neuroinflammation and other pathological phenomena may be a necessary aspect within a broader therapeutic framework.

There is a synthetic organic component [Dimethyl Fumarate], which protects nerve cells by reducing inflammation and is marketed under the name Tecfidera.[201] This component has shown effectiveness in protecting against brain damage and loss of motor neurons in the spinal cord in mice.[202] The component works by reducing the activity of proteins responsible for gene transcription [Transcription Factor] of the [NF-kB] type, which play a major role in activating inflammation in the body and are found at higher levels in the spinal cord of ALS patients. At the same time, the component increases the activity of [Nr-f2], which plays a role in cellular protection against oxidative damage.[203]

Iodine, a natural mineral essential for thyroid function and thus for metabolism, has been proven effective in reducing inflammation and oxidative damage. One study showed that iodine reduces cellular oxygen consumption (which is increased as a result of metabolic stress caused by injury), thereby lowering metabolic activity in the body. Iodine reduces

oxidative damage by neutralizing hydrogen peroxide and converting it into regular oxygen and water molecules.

Research shows that our body responds to metabolic stress by detaching iodine atoms from thyroid hormones, thereby releasing iodine that serves as a shield against tissue damage caused by free radicals. Additionally, iodine protects against tissue damage caused by systemic inflammation.[204]

A different study was conducted on epithelial cells of the respiratory system and inflammation in the mucous membrane. The study used an iodine compound [Povidone-Iodine (PVP-I)], and showed that iodine has a significant anti-inflammatory effect.[205] Iodine can be added to the list of dietary supplements that can improve the chemical-metabolic state in the body by reducing inflammation and oxidative damage.

Increased oxygen consumption can help reduce inflammation and preserve cell function. Hyperbaric oxygen therapy (HBOT) can also improve blood flow and oxygen delivery to damaged nerve cells.[206] This therapy has shown potential for treating ALS patients in clinical studies. A phase 1 safety study of HBOT on ALS patients showed significant improvements such as increased muscle strength and function, enhanced respiratory function and reduced fatigue.[207]

There are various dietary supplements designed to reduce oxidative damage and can help ALS patients return to chemical-metabolic balance. Substances such as melatonin (which I mentioned at the beginning of this chapter), coenzyme Q10, turmeric, the active ingredient in green tea [Epigallocatechin Gallate], resveratrol, vitamin E, carotenes, and various types of flavonoids.[208] A flavonoid that shows great potential is quercetin, which has shown effectiveness in reducing mitochondrial damage in animal experiments.[209] Studies show that quercetin can protect against misfolding and accumulation of SOD1 proteins in the context of ALS.[210] Other cases demonstrate that quercetin reduces neuronal death in rat experiments.[211] Furthermore, quercetin and resveratrol may be beneficial to the activity of

the Ubiquitin –Proteasome System: UPS, which is linked to the phenomena of protein misfolding, characteristic of neurological diseases such as ALS.

An antioxidant drug called Edaravone has been approved for marketing in Japan and the USA for the treatment of ALS. The drug showed anti-inflammatory efficacy,[212] and slowed the development of neurological diseases in mouse experiments.[213] However, its effectiveness on ALS patients is limited.

The established and time-tested medication (for which its Japanese inventor won the Nobel Prize) Ivermectin, apparently also has a therapeutic effect on ALS. A patent filed in 2007 claims that it was surprisingly found that the drug slows down the disease and even helps reduce damage and heal damaged nerve cells.[214] A study on mice with ALS showed that Ivermectin improves motor function and survival.[215] Another study showed that treatment with Ivermectin reduces the level of microglia activation, the immune cells of the brain and spinal cord, therefore having an anti-inflammatory effect.[216] In ALS, there is a chronic – exaggerated activation of the microglia that causes inflammation and nerve damage. Therefore, Ivermectin may help heal the disease. However, there is not enough (human) clinical data yet in order to know the extent of its effect on ALS patients.

As we have seen in a previous chapter, after the transition to rapid metabolism, there is a need for larger amounts of glutathione, but the mutated SOD protein fails to increase the amount, thus a deficiency is created. Therefore, it makes sense that giving glutathione supplements to ALS patients would improve their condition. However, there is not enough clinical information on the effects of this supplement yet.[217]

An omega-3 acid called alpha-lipoic acid is related to mitochondrial metabolism, carbohydrate (sugar) breakdown, glycogen production (the storage form of glucose in the liver and muscles) and protein metabolism. In addition, studies show that the acid has antioxidant and anti-inflammatory effects.[218] Omega-3 acids may be beneficial to the activity of the Ubiquitin –Proteasome System: UPS.

Another omega acid called alpha-linolenic acid (ALA), which is also anti-inflammatory and also protects nerve cells and brain health, has shown medical potential among ALS patients. A study from June 2023 showed that higher levels of this acid among ALS patients were associated with a lower risk of mortality, slower deterioration, and longer survival.[219]

Another omega acid called docosahexaenoic acid (DHA) is important for brain function and health, and is essential for the production and function of nerve cells. A study on mice with ALS showed that treatment with this acid can help slow the progression of the disease and lead to improvement in symptoms.[220]

A compound of amino acids called carnitine [Acetyl-L-carnitine (ALCAR)] is important for mitochondrial activity and is responsible for transporting fatty acids into it.[221] Studies show that using this compound as a dietary supplement is beneficial for ALS patients, among other things by reducing oxidative stress, helping with energy production in mitochondria, and protecting and promoting the regeneration of nerve cells.[222]

A compound called citicoline leads to the production of the neurotransmitter acetylcholine, and acetylcholine is related to an area in the brain associated with neurodegenerative diseases [dorsolateral prefrontal cortex]. Studies show that citicoline increases the amount of acetylcholine and dopamine in the brain, and protects against nerve damage.[223] In addition, studies show the effectiveness of the compound for treating a variety of neurological problems, such as dementia and nerve pain.[224] Moreover, citicoline was found to be effective in treatment of spinal cord injuries,[225] and could also be beneficial for the treatment of ALS.[226]

Beyond that, there is evidence that the absorption of basic nutritional components (such as vitamins) is impaired as part of the disease, and thus metabolism as well.[227] Studies show that the following vitamins are the most protective against the development of ALS [**vitamin B12**, vitamin E > vitamin C > **vitamin B1**, **vitamin B9** > vitamin D > vitamin B2,

vitamin B6 > vitamin A, and vitamin B7], with B12 found to be most effective.[228] Methylcobalamin is a type of vitamin B12 related to myelin, neurotransmitters, and nerve cells. This substance (which is a coenzyme) is related to the metabolism of carbohydrates, fats, and proteins. Research shows that the use of methylcobalamin in very high doses was found to be effective in slowing the deterioration in the early and middle stages of ALS.[229]

Studies show that the metabolism (and absorption) of vitamin B1 [Thiamine], which is related to energy production and neural activity, is impaired in ALS. Impairment in B1 metabolism reduces the production of the energy molecule in the body [ATP], produced by mitochondrial cells, thereby leading to neurodegeneration. A certain type of fat-soluble vitamin B1, called benfotiamine, is absorbed better than regular thiamine and has health benefits. It is possible that the use of benfotiamine can improve energy production in mitochondria and reduce neuroinflammation, thereby slowing the deterioration of the disease and improving quality of life.[230]

Miscellaneous

The importance of positive thinking, belief, and a supportive environment is great on the path to recovery. The power of positive psychology, autosuggestion, and human willpower is often underestimated. There are studies showing that positive thinking and belief in the ability to recover significantly affect the chances of recovery from severe diseases such as cancer.[231] [232] We need only examine the well-known placebo effect to understand the power of thought and belief and their impact on recovery.

The will to live and the activation of willpower to actively fight the disease can be the difference between ongoing deterioration or improvement in the condition. There are people who have managed to recover from the disease (ALS reversals), and among them are those who refused to accept defeat, found nutritional supplements/treatments that

helped them, and performed physical activity (as much as possible) to strengthen the body and activate the nervous system and muscles.

On the other hand, some of those that reversed the Neurodegeneration and other symptoms [ALS Reversal] had an innate compensatory mechanism that allows them to fight off the disease or an unusual form of ALS to start with, or perhaps they didn't have ALS at all, but were sick with an ALS mimicker [such as lime disease]. Nevertheless, some of them did have (the 'regular version' of) ALS but refused to give up and found ways to fight this terrible disease.[233]

Physical activity (as long as it's possible) is important for slowing down the disease.[234] Additionally, there is evidence that Electrical Muscle Stimulation (EMS) can benefit and improve the condition of ALS patients. A study published in 2019 showed the clinical effectiveness of Neuromuscular Magnetic Stimulation for ALS patients. The study showed significant improvement in muscle function and strength, as well as improvement in quality of life measures such as fatigue and respiratory function, among ALS patients.[235] Other forms of neuromuscular stimulation, such as Transcutaneous Electrical Nerve Stimulation (TENS), have shown effectiveness in improving the condition of ALS patients.[236]

Summary

ALS is known as an incurable disease with multiple possible causes and numerous theories about the causal factors. Some scientists focus on the genetic aspect, while others concentrate on some environmental factor, each busy in their field, making it difficult to see the big picture. Perhaps one reason for the confusion is that the disease can be "approached" from several different angles. In addition to abnormal protein folding and

genetic aspects, there may be two main pathways of environmental factors that are also interconnected and can activate each other.

Metal dyshomeostasis in the body has been linked to neurological damage, and chemical-metabolic dyshomeostasis (including impaired mitochondrial and/or liver function) has also been associated with neurological damage. It is possible that the chemical-metabolic damage is what prevents (sometimes in combination with the genetic component) the body from healing, resulting in the gradual and severe deterioration characteristic of the disease. An excellent study I found that is close to my hypothesis is the research of Nakagawa and Shizuo on metal dyshomeostasis and impaired mitochondrial function as causes of ALS.[237] I corresponded with Dr. Nakagawa, who told me that he is actually a psychologist studying the connection between psychiatric disorders and the part of the brain related (among other things) to general well-being [dorsolateral prefrontal cortex],[i] to neurodegenerative diseases and ALS. This relates to Yulia's case, to her psychological-psychiatric imbalance, which eventually led to hospitalization and deterioration of her condition after taking strong psychiatric medications.

Yulia's case is a special one where perhaps all the "necessary" components for the disease exist together: traumatic spinal cord injury, low-calorie but high-salt diet, exposure to dangerous substances due to taking medications with severe side effects (to the liver and more). There is an inflammatory component of neurological damage and inflammation, a component of metabolic impairment, and additionally the genetic component of a mutation in the C9 gene. The metal imbalance component may also be a hidden factor (blood tests reveal low levels of iron carrier and other hints), but it's impossible to know without performing an appropriate MRI. The metal imbalance component could have been caused by neurological damage following the spinal cord injury, or as a result of long-term

[i] The main neurotransmitters associated with this area of the brain are: glutamate and dopamine, and as we have seen, these play a role in processes related to the disease. Additionally, other neurotransmitters connected to this area are: norepinephrine, GABA, acetylcholine, and serotonin.

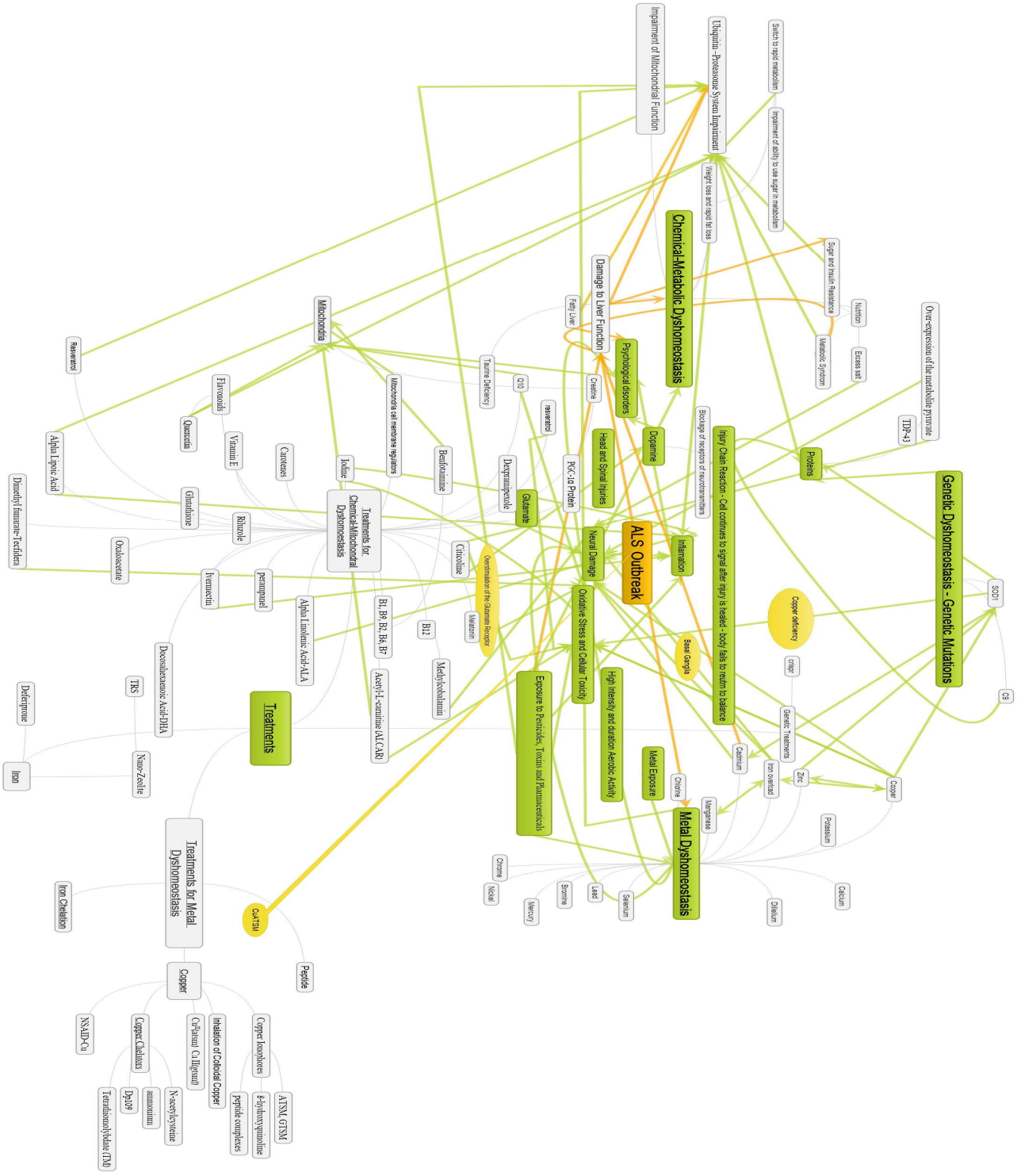
cellular processes related to diet and genetic sensitivity, or due to exposure to strong medications, or another hidden factor, or a combination of several of the above factors.

Is one factor (genetic/environmental - metal balance/environmental - chemical-metabolic balance) enough to lead to ALS? I assume not. The complexity of the disease and the statistics suggest that at least two of the three components I propose in this hypothesis are needed, if not all three together. In any case, if the medical system will know how to focus on the two environmental factors (and on the genetic factor with the help of innovative treatments such as CRISPR), perform all relevant tests and connect the information and "the dots" for each specific patient, I believe we will move quickly towards a cure for this severe disease.

We must not forget that in the history of human science and medicine, there were many difficult problems, troubles, and diseases without a cure, but through hard work and listening to the "sound of subtle silence",[j] cures were found for many of them. The Creator of the world blessed humans with many abilities and potentials that should be sufficient to turn our existence and that of our living and plant companions into nearly a paradise on earth. We need only direct our resources and efforts towards good goals, and by doing so, there is no doubt that the cure will come.

[j] Usually translated as "a still small voice" The Bible : 1 Kings 19:12

Flowchart: Causal Factors of ALS



Appendix A: Individual Experiment [N=1] and Scientific Freedom

['Scientific emancipation']

Decentralized science not controlled by aggregates of money and power

In our human world where science supposedly belongs to the wealthy and powerful – to large corporations, big pharmaceutical companies, and people of wealth and authority, the chance of reaching objective scientific Truths and/or breaking out of the existing scientific and medical narrative, consensus, and paradigm is small. Greed, corruption, and collective-groupthink keep the existing consensus and narrative in place without moving from them. For the freedom of Truth-seeking and scientific progress, science needs to be open to "the people" - to everyone. The state needs to release its centralized grip on science and develop mechanisms where every citizen can participate in the process of scientific-medical Truth-seeking.

Experiments and studies involving hundreds and thousands of participants require resources that most private individuals do not have. The process of regulatory approval for a certain treatment can take many years, and when dealing with severe incurable diseases with a very limited statistical survival time, such as ALS, this greatly hinders the ability to find a treatment in time, leaving many patients behind. It is clear that there are good reasons for long and precise processes, including safety reasons, and I am not suggesting "skipping" these processes or "cutting corners". What I am suggesting is that in order to get some hint of a theory/hypothesis regarding a specific disease and its treatment, is to perform a controlled and careful experiment on a single participant. Although the result of such an experiment will not have statistical significance, if the result is significant in any direction, it can provide a hint for a treatment path and a reason to continue with broader experiments.

An experiment with one participant is called N=1, and it is recognized by the medical community.[238] Even in the most meticulous and detailed experiments, there is no way to know for certain how a specific drug or treatment will affect a specific person (with all their personal health components). This is even more valid for patients with existing medical problems, those taking various medications, who are usually not allowed to participate in randomized controlled trials (RCTs). In a single-participant experiment, there is no such limitation, and it is possible to examine how a treatment affects a specific person, with their personal biological-medical characteristics, and to proceed in a flexible manner adapted to the individual's needs.

There is, of course, a need to know what the desired process is, to approach such an experiment in an organized manner, and to document every step. Beyond that, there is a necessity to fully inform the patient about possible risks and have them sign an informed consent form. Above all, the experimenter should ensure maximum safety, seek professional consultations and assistance, maintain complete integrity and take full responsibility for the entire process. However, courage is also needed, from both the experimenter and the patient. Because if we want to avoid staying in the same place, we need courage and daring, and to some extent, we also need to take a "leap of faith".

Appendix B: Types of MRI Tests for Metal Levels in the Brain and Spinal Cord

MRI

Gradient Echo (GRE) MRI:

1. T1 or T2-weighted images.[239] [240]

2. Susceptibility-weighted imaging (SWI).[241]

3. Quantitative Susceptibility MRI (QSM).[242] [243] [244]

4. Magnetic Susceptibility MRI.[245] [246]

GRE and other techniques:

5. MRI-based metal artifact reduction (MAR).[247] [248]

Additional types of examinations:

1. Cerebrospinal fluid test.[249]

2. X-ray Fluorescence Microscopy.[250] [251]

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