ScienceMind

AUTUMN 2022

KING'S College LONDON

TEAM

THIS ISSUE

Dear Reader,

Welcome to our Autumn 2022 issue! This issue contains articles in the categories of medicine, business/law, biochemistry, genetics, and neuroscience. Our team has been working hard during autumn to bring to you thus selection of articles. Special thanks to everyone, especially the magazine design team for bringing the articles to life. I hope you enjoy the read and make sure you follow us on social media to stay updated about future releases and events!

If this is your first time reading our magazine...
Science Mind is the award-nominated, student-led science magazine of King's College London. We report the latest findings in STEM to students and the wider community. We showcase and develop the written and oral communication skills of students interested in STEM by concisely explaining complex scientific concepts in the form of lay articles and by conducting interviews. Authors can also broaden their knowledge by writing articles for different sectors between issues.

Articles have difficulty levels. There's something for everyone!
Shallow dive: Secondary school level
Treading water: A-level to undergraduate level
Deep dive: Final year undergraduate, postgraduate, professor level

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Kind regards,

The Editor-in-Chief
Rosa Tsucala

SHALLOW DIVE

Multi Millenium Malaysian Borneo Disseverment: Earliest Recorded Surgical Operation?

WRITTEN BY CHELSEA BLAIR
EDITED BY ALEXI MERY
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In a deep Bornean cave, scientists have recently unearthed the remains of a teenager showing signs of a surgical amputation. This discovery has shaken up our current medicinal knowledge, forcing us to revisit the history of medicine.

Until present, the oldest evidence of an amputation procedure dates back to **5000 BC** and was unearthed on a Neolithic site in **Seine-et-Marne, France** back in 2010. The evidently successful disseverment in question was of an elderly man's arm, as imaging of the ancient scarred bones revealed.

Modern scientists concur that the first medical practices occurred during the **Neolithic revolution** of a decem millennium ago, where agriculture and sedentarisation brought to light previously unknown health issues. However, the excavation of human remains dating back to **24000 BC** in the Indonesian part of **Borneo** now disturbs this supposed fact by revealing that hunter-gatherers practiced surgery thousands of years earlier than estimated.

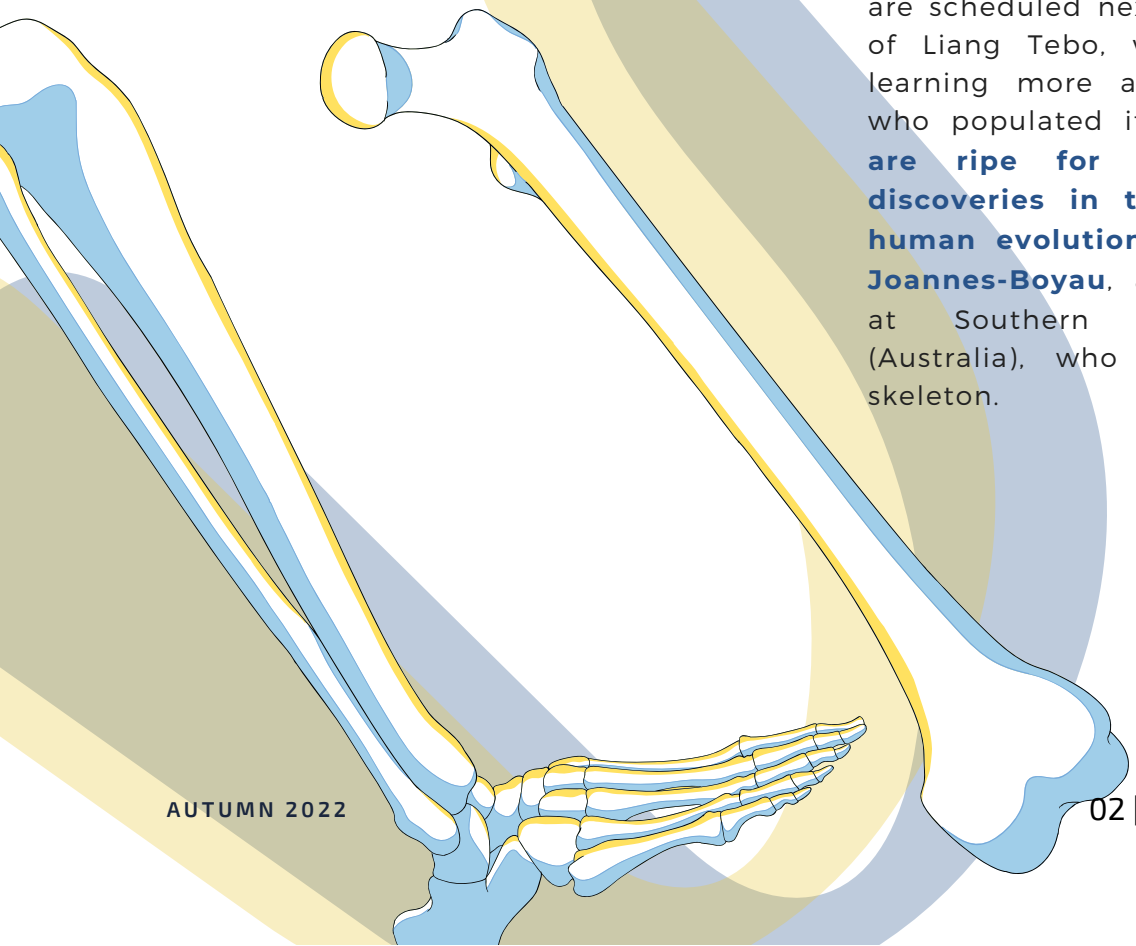
The discovery "**rewrites our understanding of this medical know-how**," states leader of the study **Tim Maloney**, a paleontologist from Griffith University in Australia. The bones had been unearthed in 2020 in the imposing limestone cave of **Liang Tebo**, known for its cave paintings.

Amongst the multitudinous bats, terns, swifts and scorpions inhabiting the cave, the paleontologists delicately removed the sedimentary layers and found the burial of a remarkably preserved skeleton missing his left ankle and foot. The end of the remaining leg bone showed a "**sharp and oblique cut, which one can see by observing the bone**", described Tim Maloney. Had this cut been caused by a fall or an animal attack, this appearance would have been less regular hence why this appears to be a surgical procedure.

ANATOMICAL KNOWLEDGE

The patient seemed to have **survived** an astonishing **nine years post-intervention**, which was illustrated by the signs of **observable bone repair** under a microscope. Moreover, it is unlikely that the amputation was performed as a punishment, as the young adolescent appears to have received **careful post-surgical treatment**, including at the burial.

"**This presupposes an in-depth knowledge of human anatomy regarding both the muscular and vascular system**", the study states. The individuals operating on the young teenager had to "**regularly clean, disinfect and dress the wound**" in order to prevent any postoperative bleeding or infection that could lead to death. Not only that, but the physical state of the young diminished amputee also suggests that those around him **supervised** him for the nine year to come, testifying to an **altruistic behavior** among this group of hunter-gatherers.



This work "**sheds new light on the care and treatment provided in the distant past, and upsets our view that these questions were not taken into consideration during prehistoric times**", reacted **Charlotte Ann Roberts**, an archaeologist of the British University of Durham who accompanied the study. In terms of surgery, although there are numerous prehistoric traces of trepanation or pulling of teeth, **limb amputations are extremely rare** as they are difficult to identify on poorly preserved bones; it was suggested that cut stone blades were used to proceed with operation. In the tropics, the **rapidity of infections** may have spurred the **development of antiseptic products** exploiting the medicinal properties of Borneo's rich vegetation, the scientists argue.

After this Bornean discovery, many questions remain unanswered: **how did they proceed? Was this a practice common? How did they relieve the pain?** New excavations are scheduled next year in the cave of Liang Tebo, with the hope of learning more about the humans who populated it. "**The conditions are ripe for astonishing new discoveries in this 'hot spot' of human evolution**", assures **Renaud Joannes-Boyau**, associate professor at Southern Cross University (Australia), who helped date the skeleton.

References

TREADING WATER

Healthcare management in low income countries

WRITTEN BY SHREYA KAUSHIK
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Healthcare management can be defined as the supervision of any healthcare setting (direct or indirect) through managerial roles in order to optimize the service of healthcare to the general public. The **Bureau of Labor Statistics** referred to healthcare management as one of the "**fastest growing occupations** in the world." The healthcare industry has to adapt to fast-paced changes and the vast majority of the population grasped the importance of efficient healthcare management during the SARS-COV-2 pandemic. However, just the realization is not enough and the knowledge deficit within this market has to be supplied with a professional workforce. Healthcare management is essential in making sure that the levels of funding are constantly appropriate to the demographic epidemiological curve, technology innovation curve and citizen expectations. A review of 37 studies conducted reflected the direct correlation between efficient leadership and managerial roles and the performance of healthcare practices.

Healthcare can't be grasped on a general scale and healthcare systems have to be understood on a regional basis. Different countries provide their citizens with healthcare with varied approaches. **France** was ranked as the **most advanced country in medicine and healthcare** by the World Health Organization due to its universal coverage and statutory health insurance introduction to every citizen in 2000.

However, the COVID-19 pandemic negatively impacted the healthcare system of various countries including the routine care for chronic diseases such as hypertension, diabetes, trachoma and leishmaniasis. **The Global Liveability Index** suggests that the healthcare infrastructure in cities such as Jakarta, Prague and Athens have worsened.

It makes us wonder if the management of developed countries respective or irrespective of a pandemic is so arduous, how do underdeveloped countries manage healthcare? The organization direction and fiscal resources these countries lack need to be addressed.

Due to the lack of necessary funds and receiving zero to minimal healthcare, around **100 million people** are pushed below the poverty line in these low income countries. A community and household in a low income country requires effective interventions but lacks it due to physical, social and financial constraints. An approach to this issue could be to financially incentivise healthcare so that minority groups in poverty-stricken households might come together to raise awareness or spread information about healthcare issues in underdeveloped parts of the country.

Poor healthcare management results in substandard healthcare services as a result of the inefficient infrastructure and accessibility of these services. Nevertheless, a managerial response to incompetent service delivery may focus on strengthening the healthcare team.

A case study published in a case series called **Social Innovation in Health** covers an extremely interesting aspect of healthcare management where childhood illnesses in underdeveloped countries are governed through integrated management of drug shops. **The Drug Shop Integrated Management of Childhood Illness project** was a pilot programme that aims to overcome barriers in healthcare management by evaluating the effectiveness and feasibility of incorporating the welfare of the children in Uganda with drug shop owners in the private sector.

This allows young individuals to be able to access **private healthcare** for the treatment of **diarrhea, malaria and pneumonia**. Several drug shop owners from private sectors were given subsidized medical supplies, integrated community case management training, and diagnostic equipment such as rapid diagnostic tests.

This case study acknowledges the inefficiency of the managerial aspect in healthcare and aims to combat this through management training of private healthcare workers in the context of public healthcare in Uganda. It also opens doors to new opportunities for collaborations to implement enhanced healthcare through effective management in the future.

Increasing the number of staff, pay, training, supervision and utilizing the private retail system aid in improving the inadequacy of delivery of medical supplies and drugs. The healthcare sector deals with weak policy and strategic management such as weak regulation of the pharmaceutical industry, inadequate drug policies and unduly centralized management systems. This can be overcome by **decentralizing** these **management systems whilst instituting new legal and supply mechanisms.**

"It excites us a lot that we've shown a way to engage with this group of drug shops and actually harness their potential for improving outcomes in child health." **- Phyllis Awor**

References

DEEP DIVE

The answers behind the most potent toxins known to man

WRITTEN BY ADELINA KRUSTEVA
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Botulinum toxins (BoNTs), the most poisonous biological substances known to mankind, are produced by ***Clostridium botulinum***, a **spore-forming anaerobic bacteria** and are well known for their use in cosmetic procedures. However, their property to act upon different **SNARE proteins** is used in medicine to **treat movement disorders, muscle spasms or eye disorders** such as blepharospasm, (uncontrolled blinking) or strabismus. Among the various therapeutic applications found in recent years, BoNTs were discovered to provide support in **cancer therapy**. The limited literature data suggests that cancer cell lines' growth and mitotic activity is reduced, and its apoptotic cell death escalated with addition of BoNTs to the cell culture. In addition, there were no systemic side effects observed upon administration of the potent toxins. Thus, making BoNTs a desirable future target for **new classes of anticancer drugs**.

The **structure** of BoNTs is crucial for its multifaceted function. There are **seven different BoNT serotypes/components**, expressed by letters A to G. There are more than 40 subtypes recognised among the 7 (A-G) serotypes.

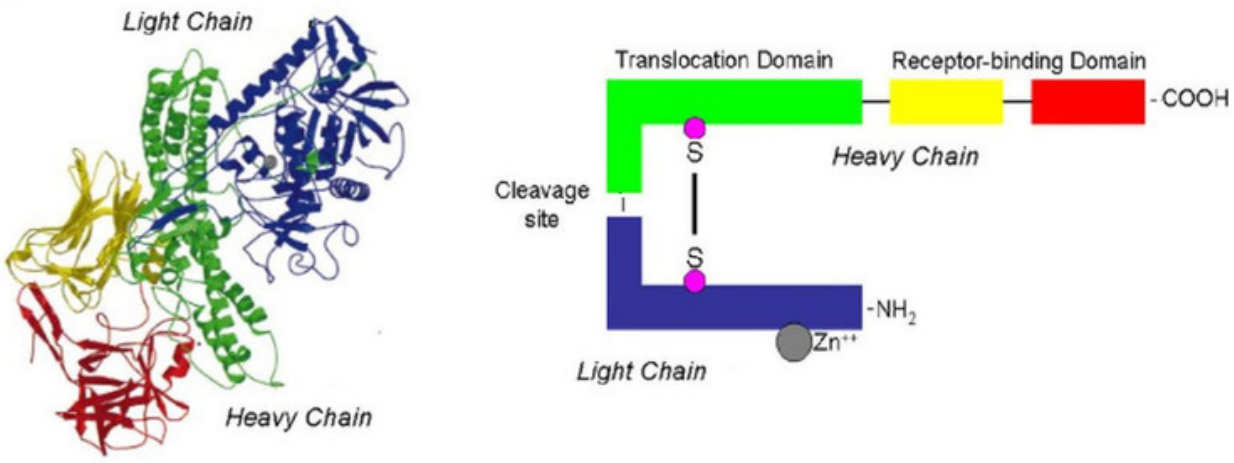

Figure 1. The distinct structural components of BoNT. A) The diagram shows the different domains in the light and heavy chain, as well as the cleavage site. B) The molecule is presented in a 3D construct highlighting the dimensional configuration of the toxin. (Lebeda et al., 2008).

The seven types of BoNTs share a similar molecular weight and structure. The main body construct of BoNTs consists of a **light** (LC, 50kDA) and a **heavy chain** (HC, 100kDa) joined by a **disulphide bond** (**Fig.1B**). The action of the neurotoxins originates due to the specific structure of the HC, which binds to **polysialogangliosides** (PSGs) on the cell surface of the **presynaptic cholinergic neurons**. Thus, inhibits the SNARE proteins, leading to the **prevention of acetylcholine release** by the light chain subunit.

After the protein internalisation, BoNT **resides within the synaptic vesicle**. The **influx of H+ ion** is originated by vesicular proton pumps, which then acidifies the vesicles. Subsequently cytosolic ACh is imported and concentrated within the vesicle through **ACh transporter protein activation**.

Following, the **N terminal of the HC** (translocation domain) (**Fig.1A**) **translocates the LC** to the cytoplasm from inside the vesicle. While bound to the rest of the protein the LC is inactive, but when translocated and released by cleaving enzymes such as thioredoxin reductase–thioredoxin system (TrxR-Trx) and heat shock protein 90 (Hsp90), is **activated to cleave SNARE proteins**. SNARE proteins such as SNAP25 (synaptosomal-associated protein, 25 kDa), VAMP (vesicle-associated membrane protein) and syntaxin (Stx) are **essential for vesicle fusion with the presynaptic membrane** and **exocytosis of acetylcholine**. The introduced SNARE proteins are a target for various BoNTs. SNAP-25 cleavage is determined by BoNT/A while BoNT/E, BoNT/B, BoNT/D, BoNT/F, BoNT/G, and BoNT/X are accountable for the cleavage of VAMP, SNAP-25 and syntaxin are cleaved by BoNT/C (**Fig.2**).

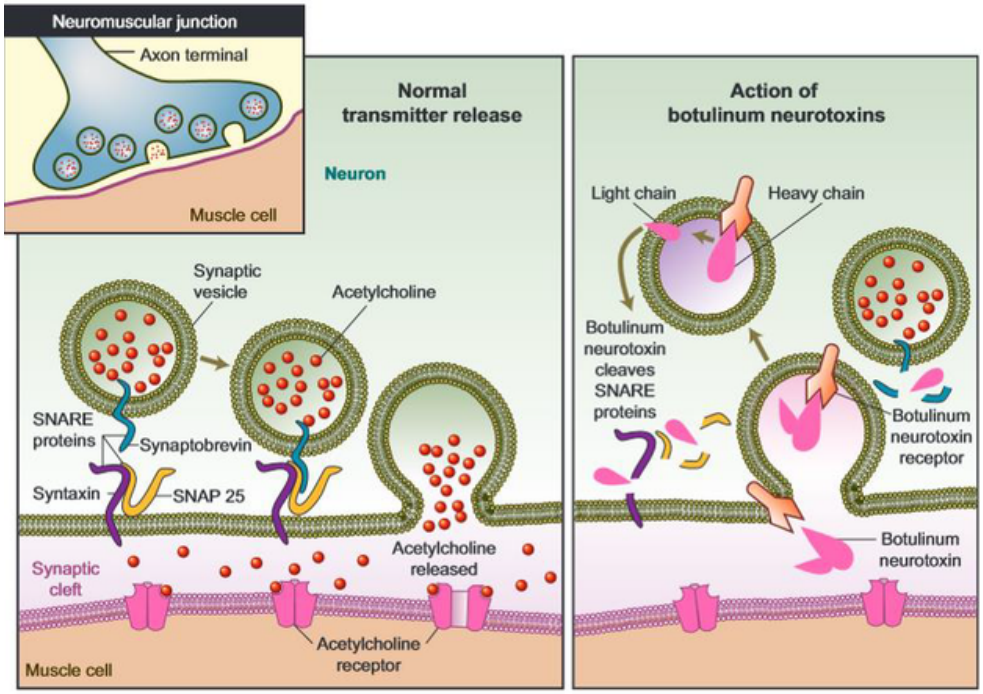

Figure 2. Comparison between normal cell vesicle docking and release of acetylcholine vs. the blocked neurotransmitter exocytosis by the light and heavy chain of BoNT. The individual stages of BoNT intoxication including recognition of the surface, internalization of vesicles, light chain translocation and SNARE protein cleavage. The VAMP family is shown in blue, SNAP-25 in yellow and syntaxin is colored in purple. (Rowland, 2002)

In the last two decades, the development of innovative neoadjuvant treatment has led to cancer treatment results with improved life quality and long overall survival. Therefore, it is vital to new methods which can support patients' recovery after tumor removal surgery and assemble their further treatment. **Botulinum toxins**, despite being the most potent toxins known to mankind, **own the properties to be used in oncological treatment**.

In vitro and in vivo studies have recently discovered that **BoNTs play a key role in tumor size reduction and cancer cell apoptosis**. These studies were conducted using human or animal models with direct BoNT application. The cell lines used for the experiments were derived from tumors such as colorectal cancer, breast cancer, pancreatic cancer or endocrine tumor.

One of the earliest studies performed by **Huang et al.**, (1998) displays an outbreaking discovery performed with insulin-secreting HIT-T15 cells. The results showed that **transient translocation of BoNT/A into SNAP-25 can regulate insulin secretion**. Therefore, it can be concluded that BoNT/A can be used in the treatment of endocrine tumors.

A decade later an experiment by **Karsenty et al.** (2009) included control cells with no exposure to BoNT and BoNT/A exposed PC-3 and LNCaP cell lines (prostate cancer cell lines). The researchers observed that the toxin increased apoptosis and reduced LNCaP cell proliferation while PC-3 cells were not affected. The target of the neurotoxin, SV2 (synaptic vesicle glycoprotein 2) was present in both cell line LNCaP and PC-3 in a ratio of 4:1, respectively.

It was discovered that 28 days after treatment with BoNT, cell growth decreased significantly compared to control cells. Therefore, it was suggested that **BoNT/A might induce apoptosis in the cell lines**.

As a third example, **Bandala et al.** conducted two studies in 2013 and 2015 regarding the influence of BoNT/A on breast cancer cell lines (T47D). The first study demonstrated that the **neurotoxin induced caspase-3 and -7** (apoptotic process) in the **cancer cell lines** and showed no cytotoxic activity in the control cells.

The results of the previously mentioned experiments show an **effective use of BoNT constructs in cancer treatment.** The knowledge of safe utilisation of the neurotoxins as well as new constructs of non-toxic BoNTs have appeared in scientific papers. However, there are still doubts linked with the toxins' construct and its relative functions. In summary, **BoNT is recognised as a new target for research and use for oncological therapy**, hoping to become the answer to one of the deadliest conditions.

References

TREADING WATER

Control your genetic destiny with Epigenetics

WRITTEN BY PRACHI PURANIK | EDITED BY ANDREA MAZGALEVA | DESIGNED BY ASHNA SURANA

Imagine sharing your life with a person who seems to be you, created from the same fertilised egg and share exactly the same genes. But even identical twins can grow up very differently at a functional level, one with autism and one without. So, if genes don't tell the whole story of who we are then what does?

The answer lies in a vast chemical network within ourselves that controls our genes, turning them on and off.
In the 1990s the greatest international scientific research called the **Human Genome Project** was undertaken. By decoding the human genome scientists hoped that the genetic cause and cure for every disease would be in our hands. But as the project neared completion, it appeared that humans had around the same number of genes as fish or mice. This baffled them as it didn't explain the human complexity.

Scientists then observed two interesting syndromes: **Angelman syndrome** and **Prader-Willi syndrome.** They both were caused by the exact same deletion of a key sequence of DNA in chromosome 15 but had very different symptoms. To determine how this was possible, it was further investigated. It was discovered that despite the key sequence being identical, different sets of genes were being silenced depending on whether they were maternal or paternal. This suggested that there must be a chemical tag or imprint on **chromosome 15** for the gene to know where it came from.

This was the first evidence that something which could control genes directly was passed between generations.

How do tags silence a gene?

There are many ways that gene expression is controlled in eukaryotes. A very important one is a chemical tag called a methyl (-CH3) molecule which attaches to the cytosine base of DNA. Methylation plays a crucial role in **decreasing** gene expression, by blocking the promoters where activating transcription factors should bind. Other tags such as histone acetylation change the chromatin architecture and **increase** gene expression by relaxation of chromatin. These tags control gene expression and are a part of the **epigenome.**

Epigenetic Phenomenon

There is no genetic difference between the cells of the eyes and the cells of the teeth, but they still make up very different tissues. What distinguishes cells is not their genes but how these genes are switched on or off by epigenetics. The switches are usually very stable but are reversible, and occasionally some epigenetic switches can be reversed.

The tale of two agouti mice

Despite the difference in colour and size, these two mice are **genetically identical twins.** In the yellow mouse, the agouti gene is overactive and is turned on all the time. It inappropriately blocks the receptor in the satiety centre of the brain which tells mice and us when we're full. So yellow mice tend to eat uncontrollably and develop obesity and diabetes. On the other hand, the thin brown mouse had a methyl tag near the agouti gene which **suppressed transcription** of the gene. To turn off the overactive agouti gene in the yellow mouse, overweight pregnant mothers were given foods rich in B-12 or folic acid from which they could make those methyl tags that silenced genes. Soon they gave birth to thin brown pups no longer prone to the disease. This showed that early stages of development in the womb are linked to adult disease susceptibilities by changes in the epigenome.

Fig 2 - The colour of the skin depends on the methylation state of a sequence present near the agouti gene responsible for the colour: in the methylated state, the Agouti gene is suppressed, the colour will be brown, but in the demethylated state, the gene is overactive and leads to a obese, yellow mouse.

Experiences can change the genome

If a child grows up in a family that involves abuse, neglect, harsh and inconsistent discipline then they are statistically more likely to develop depression, anxiety and drug abuse. What is surprising is that even certain diseases like diabetes, heart disease and obesity are more likely to develop. Stress hormones actively promote the development of these individual diseases.

In a study (Weaver et al., 2004), rats born to nurturing mothers who licked and groomed them intensely after birth were compared to rats born to low licking mothers. Both the offspring line were compared in stressful events. Offspring of low licking mothers during periods of stress showed greater increases in blood pressure and stress hormone production. The particular gene responsible for lowering the levels of stress hormone in the blood were compared in low and high licked rats.

Less nurtured rats had multiple epigenetic marks silencing the gene that helps lower stress. As a result, stress levels in neglected rats soared. Whereas nurtured rats could better handle stress because there was no silencing of the gene. Removing these epigenetic marks in low licked rats with a drug changed the behaviour of the rats and they were better able to handle stress. This suggested that **maternal behaviour** played a **key role in epigenetics**.

Transgenerational effect

Taking these results further, a study (Heijmans et al., 2008) was conducted in humans from the Dutch Hunger Winter in 1944. It showed that the availability of food to the people affected in the Dutch hunger winter was affecting the mortality rate of their grandchildren.

Certain periods during which an organism is more susceptible to epigenetic changes through environmental influences are called **sensitive periods**. It turns out that sensitive periods for a female are different than that of a male.

The grandmother was susceptible to epigenetic changes while she herself was still in the womb during the period of famine. The grandfather was susceptible to epigenetic changes when he was in his late childhood during famine. The timing of the sensitive periods tells us that epigenetic changes were tied to the formation of the eggs and the sperm of the grandparents. Environmental information was being imprinted on the egg and sperm at the time of their formation.

Men who experienced famine around age 10, had paternal grandsons who lived much longer than those whose grandfathers did not experience famine. Women who experienced famine while in the womb had paternal granddaughters who died on average far earlier. This transgenerational response is only known to occur in the paternal line of inheritance. These results have puzzled many researchers and left several questions unanswered, for example, why is famine both beneficial and harmful depending on the sex and age of the grandparent affected and why is it only in the paternal line of inheritance?

Generations to come

Today we are aware that our lifestyle choices can potentially affect people yet unborn. The hurdle is that unlike the genome, which is the same in every cell, the epigenome varies from tissue to tissue between individuals over time. To understand epigenetic diseases further it is essential that we take an initiative to map the epigenome, similar to the Human Genome Project, which could tell us more about how genes are regulated in cells. **Epigenetics has changed the way we think about inheritance forever.**

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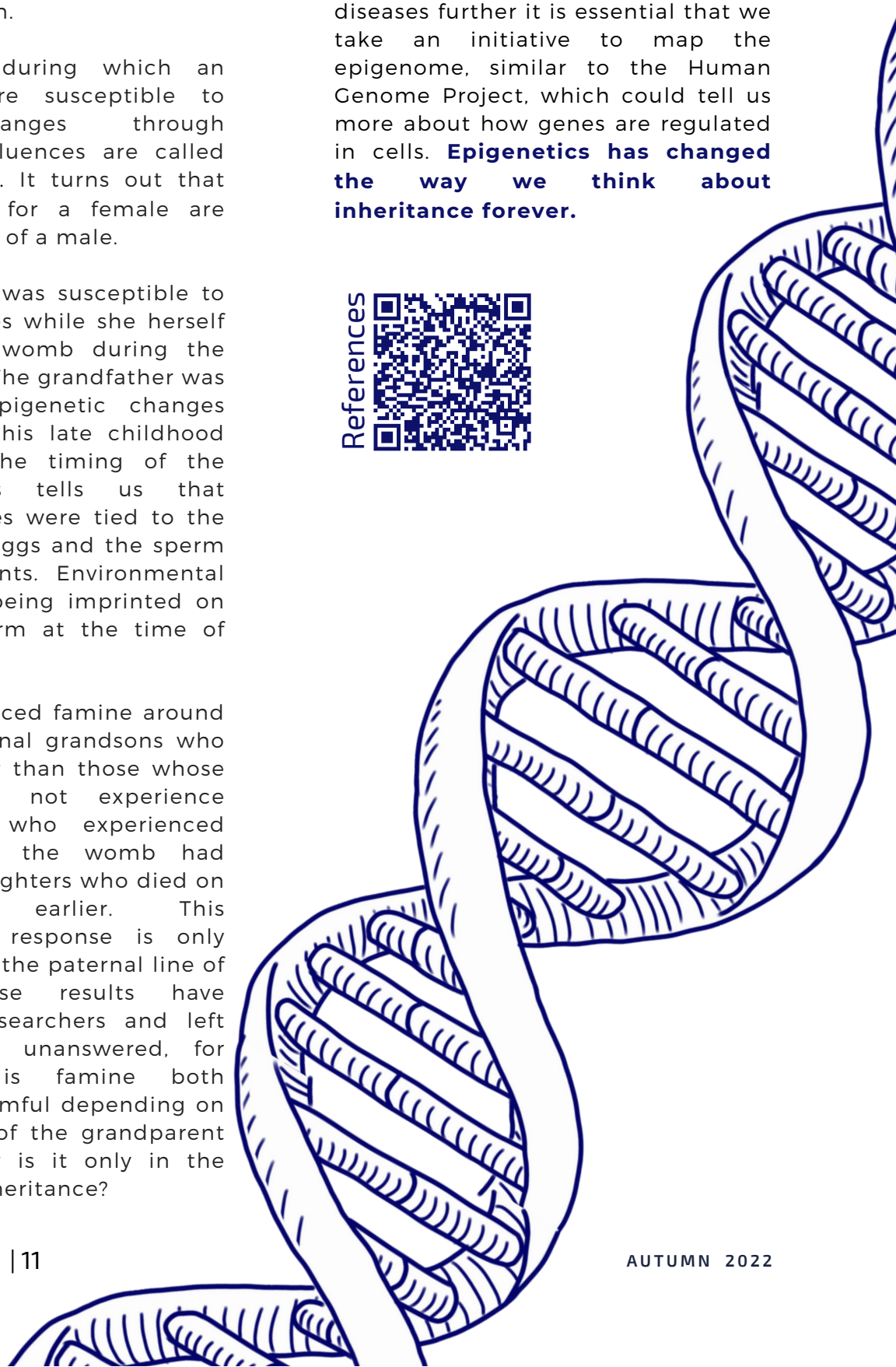

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TREADING WATER

iPSC-based GWAS discovers a novel susceptibility locus for viral infections

WRITTEN BY VIDUR TANDON | EDITED BY ANDREA MAZGALEVA | DESIGNED BY ALICE KOSMIDER

Oftentimes understanding the underlying genetics of a disease can be quite complex. A useful assay to determine which genomic variants cause a certain common disease or phenotype is genome-wide association studies (GWAS), most commonly focusing on single-nucleotide polymorphisms (SNPs) that are statistically significant to the phenotype (Uffelmann et al., 2021).

Normally a vast number of individuals are necessary in studies such as GWAS as it is important to accumulate appropriate **statistical power** for the results to be as precise and correct as possible. This large-scale endeavour is combined with high costs and tends to be labour intensive. While research has been conducted to better apprehend genetic susceptibility to **infectious diseases** via genomic variants, this nevertheless presents significant challenges due to cases and controls not being adequately defined. Therefore it may provide more indicative results if the infection were performed in the laboratory, to be able to gauge pathogen susceptibility.

One research group used **induced pluripotent stem cells (iPSCs)** which carry stable genomes of their original donors, and performed a GWAS on these. This allowed for reduction in **variability** between the samples allowing for a smaller sample size as well as having the possibility of differentiating the cells into the **disease-relevant** cell types. The primary investigated virus was the **Zika virus (ZIKV)** (Han et. al., 2022).

The iPSCs were derived from 77 individuals and were infected with ZIKV. To validate the iPSC based assay, the research group also differentiated some cells into **cerebral organoids** containing neural progenitor cells which are involved in a certain ZIKV phenotype. Both the iPSC cells as well as the differentiated cells had a high percentage of **viral RNA** as well as the ZIKV **envelope protein** ZIKV-E+. NDUFA4 was identified as a **locus** of interest by analysing and genotyping almost 700,000 SNPs in the genomes of the iPSCs. Out of these, 10 SNPs with the strongest **linkage disequilibrium** were found to be in a region where only NDUFA4 was expressed and had high expression in those cell lines that were highly permissive to the virus.

NDUFA4 encodes for a **mitochondrial protein** whose function is thought to be a component of cytochrome c oxidase which is essential in the electron transport chain. A mutated version is connected to neurological disorders such as Tourette syndrome. When the gene was knocked out using a **CRISPR**-based method, the cells were less susceptible to the virus. Looking more closely at the role of the gene showed that in iPSCs, as well as in the differentiated neural progenitor cells, the gene is responsible for viral RNA **replication**. To continue, they investigated another flavivirus, the **Dengue virus (DENV)** which similarly to ZIKV also displayed higher permissiveness in those cell lines with the risk alleles that were shown to cause increased susceptibility to ZIKV. This was also tested with a non-flavivirus, **SARS-CoV-2**. In this case iPSCs were differentiated into **lung airway organoids**, with the same results as before. A further observation showed that higher levels of NDUFA4 expression was detected in lung tissue derived from **COVID-19 patients** than from healthy donors, as well as higher expression in severe infection than mild patients. Their final observation indicated that loss of NDUFA4 causes mitochondrial stress and mtDNA leakage leading to **type I interferon** upregulation which subsequently leads to **protection** against the virus and represses its replication, although it does not completely block the infection (Han et al., 2022).

The use of iPSCs in mimicking traditional GWAS still needs refining, as expected. Of course the permissiveness of these iPSCs and their derived cells cannot be translated directly to the general population, and there are always other aspects that need to be considered such as age or environment that increase variability. However, it does make the process of GWAS more efficient and has proved to show results, as seen with NDUFA4. This finding will undoubtedly be useful in future research, especially when considering the COVID-19 pandemic.

References

The majority of people think of migraines as a form of headaches. However, this is a mistaken belief. A migraine is a neurological disorder that mainly **differs from headaches in the area that the pain spreads through**. Headaches largely affect the regions of the head and neck, while migraines cause a throbbing pain sensation in **one side of the patient's head**. Other symptoms of a migraine include nausea, increased sensitivity to light and sound and mood swings. However, this article is going to focus on one of the most overlooked migraine repercussions - **major depressive disorder** (MDD). It will discuss their relationship and explain some of the physiological mechanisms involved that draw a link between these disorders.

Migraine symptoms frequently **develop a few hours before the hemicranial pain begins**. However, there are cases when the first symptoms may appear even a couple of days before. Migraine attacks develop in **4 stages** over a period of time (Fig. 1, 2021).

The stages are:

1. **Prodrome** - develops a few hours to a few days before the migraine starts, with little severity.
2. **Aura** - starts between 5 to 60 minutes before an episode with mild pain severity
3. **Migraine episode** - high severity
4. **Postdrome stage** - 24 to 48 hours after the attack. This is the recovery period when aching reduces, but does not cease completely.

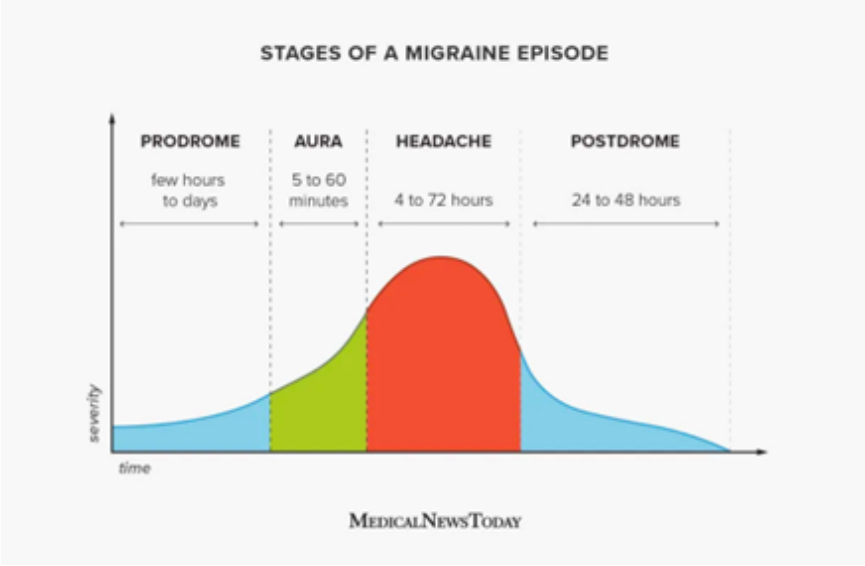
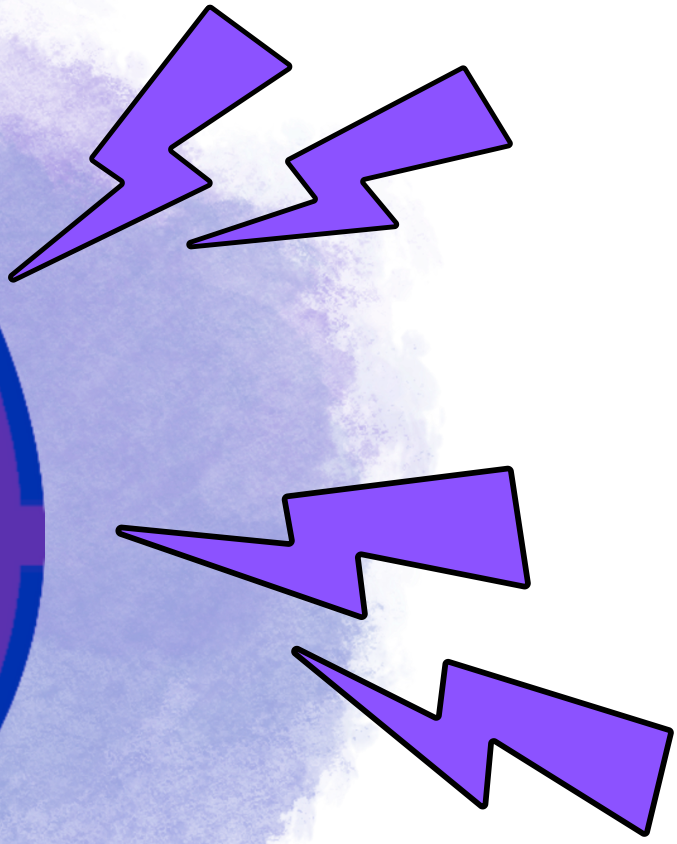


Figure 1. Timeline graph representing the 4 stages of a migraine episode development, and the pain severity (y-axis) during those stages

Depression, on the other hand, is most described as a **mood disorder that affects an individual's perception of the world**. Patients suffering from MDD experience difficulties when performing daily tasks such as sleeping, eating, and working. The aetiology of MDD is still not clear. However, there is evidence suggesting that it is a **result of both environmental and genetic factors**. In this article, we will explore **migraines as a potential aetiological factor** that might trigger MDD.

Dawn Buse, director of behavioural medicine at the Montefiore Headache Centre, stated in an interview that "About 1/3 or 1/2 of those suffering chronic migraines may develop anxiety and/or depression" (American Migraine Foundation, 2018). The interview postulates that although one might not necessarily cause the other, it is thought that **both migraines and depression set off the same biochemicals in the brain**.

So how could migraines trigger MDD? The relationship is not direct, nevertheless, there are series of events where one could eventually lead to the other.



The correlation between Migraines and Major Depressive Disorder: is there a link?

WRITTEN BY ZARINA KOZHAKHMETOVA
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DESIGNED BY WINNIE WING YIN LIU

TREADING WATER

AUTUMN 2022

Hormonal Theory

One of the most common triggers for a migraine is **stress or other negative emotions**. This is explained by the fact that the muscles in the back of your neck and scalp tense up when angry or upset (NHS, 2021). Therefore, **depressive episodes may also result in migraine attacks**. However, we can observe an even closer link. Some studies have demostrated that migraines can be **caused by low serotonin** (the messenger hormone) **and oestrogen** (sex hormone) levels. Statistics show that women are 2-3 times more likely than men to have migraines at any given age (Fig. 2, 2020).

Similarly, women are nearly twice as likely as men to develop depression (Fig. 3, 2019). Hence, it can be suggested that there is correlation between the data.

Multiple sources (John Hopkins Medicine, 2012) state that oestrogen has a **direct effect on the activity of sensory neurons** in the peripheral and central sites of the human organism. Women experience hormonal fluctuations regularly, especially at different points of maturity. A **sudden drop in oestrogen level evidently increases sensitivity to pain**, but the exact pathophysiology of this process is yet to be investigated (Chen et al, 2021).

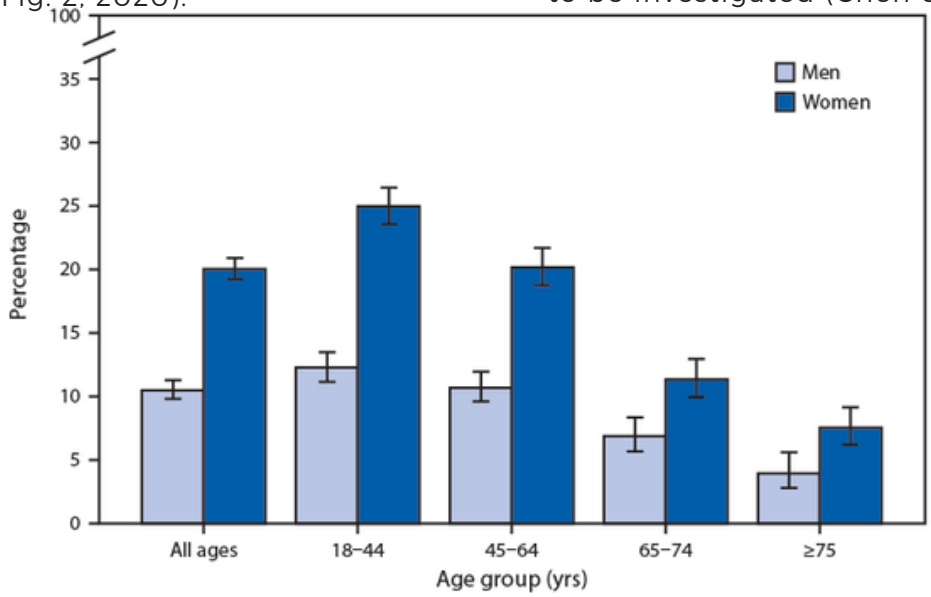

Figure 2. Bar graph comparing the worldwide percentage frequency of reported migraine cases among men and women between the ages of 18 and 75 in 2020.

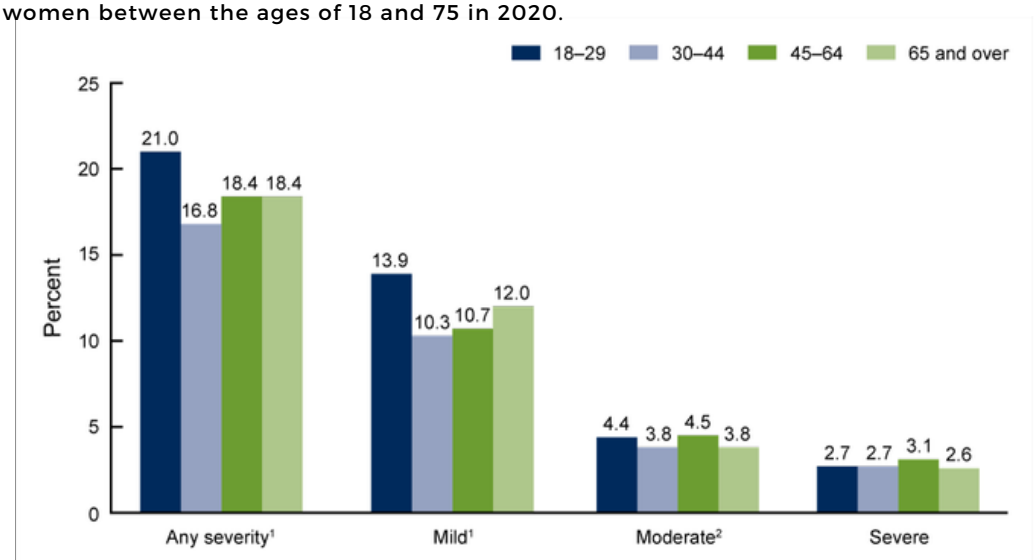

Figure 3. Bar graph comparing the worldwide percentage frequency of reported depression cases among men and women between the ages of 18 and 75 in 2019, and the case severity (mild to severe).

Vascular Theory

Another theory proposed is related to the mechanisms of the vascular system. Oestrogen is not only a **vasodilator**, but also a **hypotensive agent**. This means that apart from relaxing the vascular smooth muscle, it also opposes the vasoconstrictor response to various stimuli (Lahm et al, 2008). This is achieved through the **stimulation of the endothelium**, which in turn releases substances, such as nitric oxide, that cause vasodilation. During periods of low oestrogen levels, the human organism becomes more vulnerable to external triggers. Accordingly this leads to the **narrowing of the blood vessels thus restricting blood flow** and therefore the development of a migraine.

Likewise, oestrogen seems to have a direct effect on serotonin. Serotonin hormone is particularly associated with the part of the brain's nervous system that controls mood and emotion. Studies show that **decreased oestrogen levels lessen the frequency of successful binding of serotonin to the receptor sites and lower its activity**. Hence, one may experience **mild to severe mood swings** that could further **progress into MDD episodes**. However, current research has not yet substantiated this theory. Low serotonin levels can only be **linked to depression non-directly**, especially if the patient has a history of the disorder.

Although the relationship between a migraine and depression is yet to be investigated, the theories discussed today may be critical towards elucidating this mystery. **Further research on their correlation** could expand our understanding of their **origin and potential cure**. The investigation could start from looking at the **mechanism of action of oestrogen at sensory neurons** and then proceed into **examining whether serotonin and oestrogen can be associated** with one another. However, until then, patients suffering from migraines will be prescribed painkillers or triptans. Whereas individuals with major depressive disorder will be treated through psychotherapy and in some cases medication.

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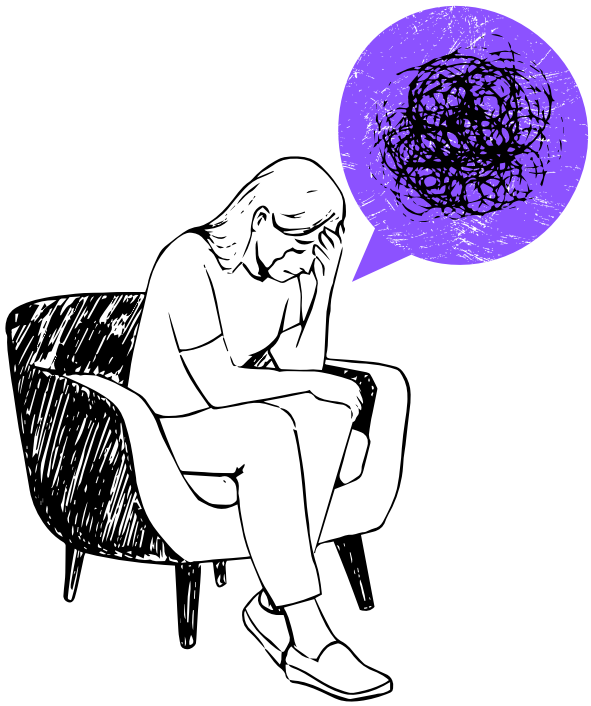


TREADING WATER

How can novel combined stem cell-gene therapy possibly curb ALS progression?

WRITTEN BY WAI IN NG, JANINE
EDITED BY ELINA SUTER
DESIGNED BY DORIS YU

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease. Due to impaired motor neurons in the brain and spinal cord, patients with ALS lose their ability to control voluntary movements and may eventually become paralysed. They are usually subjected to a variety of debilitating symptoms including cramps, spasticity and respiratory insufficiency. Advances in the field of genetics have undoubtedly improved the knowledge behind ALS, including its causes and therapeutic development. Yet, this disorder has been regarded as **incurable** from a clinical perspective because of its seemingly irreversible progression.

Recently, new therapeutic strategies ranging from gene-editing technologies to mRNA-based medicines are being developed. It is known that **dysfunctional astrocytes** play a key role in the pathogenesis of ALS. **Glial-cell-derived neurotrophic factor** (GDNF) is a potent growth factor which is crucial in the **regeneration of damaged motor neurons**. Cedars-Sinai investigators transplanted **engineered stem cells** into the **central nervous system**. These cells are responsible for replacing diseased astrocytes and releasing GDNF. After this one-time treatment, the **degeneration of the motor neurons can be reduced**. This may improve mobility and thus the quality of life of the patients.

The causes of ALS are incompletely understood, but it is suggested that **genetic and environmental risk factors** contribute to the development of ALS. The former factor gives rise to **approximately 60% of the risk** of the disorder. ALS can be classified into **familial** (fALS) and **sporadic** ALS (sALS), accounting for 10% and 90% of the cases respectively. **Chromosome 9 open reading frame 72** (C9orf72) mutation is indicated to be one of the common variations among ALS patients. Recent studies have emphasized its importance in both fALS and sALS pathogenesis. A high frequency of the pathogenic **GGGGCC hexanucleotide repeat** in the gene C9orf72 is believed to be strongly associated with the disease. A study by **Birger et al.** (2019) utilised human induced pluripotent stem cell-derived astrocytes from ALS patients carrying C9orf72 mutations.

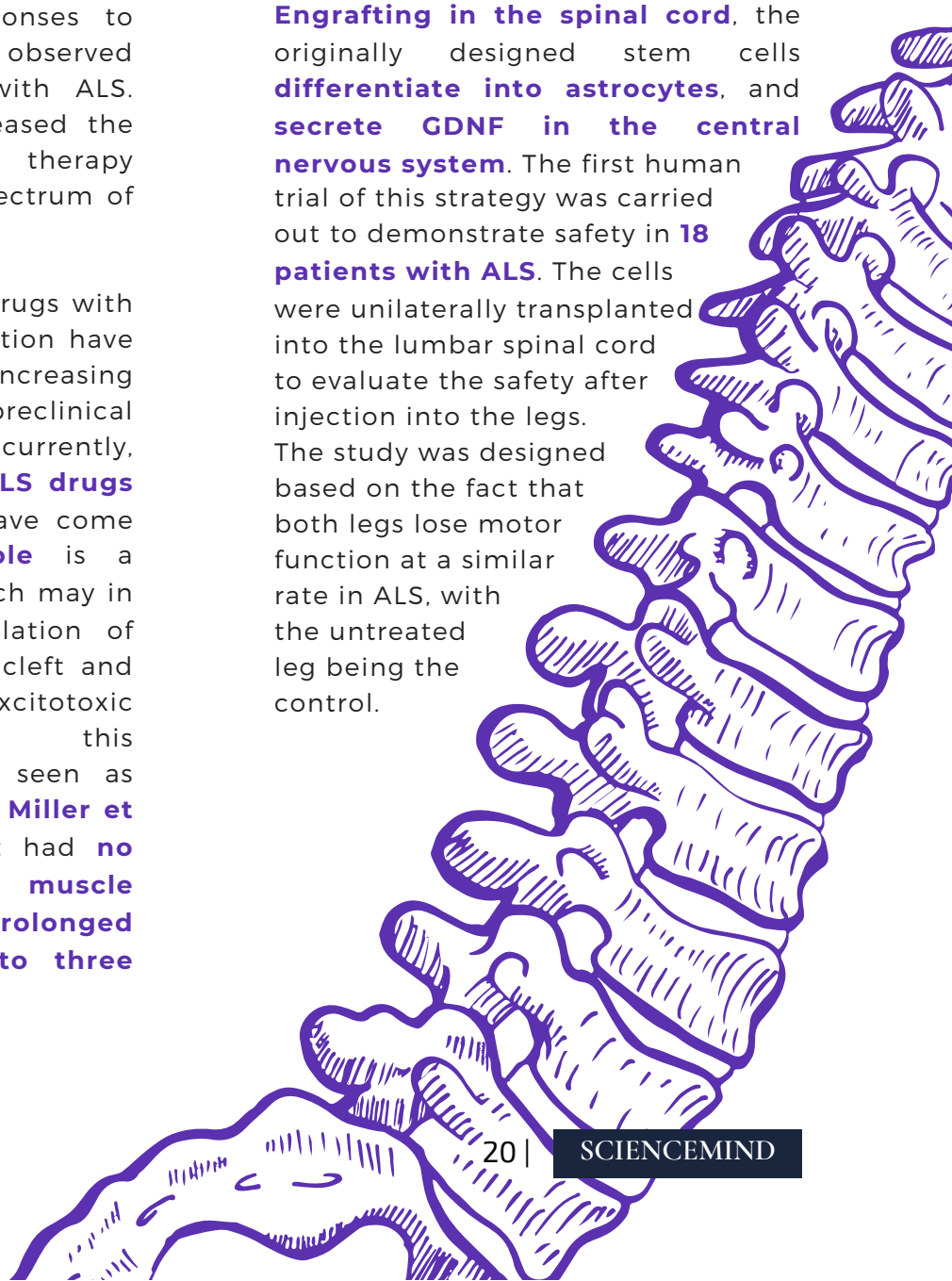
When the mutated C9orf72 gene is expressed in astrocytes, the **expression of several antioxidant proteins is downregulated**. These astrocytes may fail to exert protective effects on motor neurons, resulting in neurodegeneration.

Although a multitude of research has proposed that several altered signalling pathways such as glutamate excitotoxicity and mitochondrial dysfunction are involved, the **underlying pathogenetic mechanisms remain unclear**. Hence, current therapeutic approaches only have minimal effects on the survival of the patients. Besides, owing to genetic heterogeneity, varied responses to similar treatments are often observed among the populations with ALS. This has significantly increased the difficulty in developing a therapy applicable to the entire spectrum of phenotypes seen in ALS.

A wealth of experimental drugs with different mechanisms of action have demonstrated efficacy in increasing the life expectancy in preclinical animal models of ALS, but currently, only **two FDA-approved ALS drugs** (riluzole and edaravone) have come onto the market. **Riluzole** is a **glutamate antagonist** which may in turn prevent the accumulation of glutamate in the synaptic cleft and thus the trigger of excitotoxic processes. Though this antiexcitotoxic strategy is seen as neuroprotective, a study by **Miller et al.** (2012) suggests that it had **no effect on enhancing muscle strength** and only **prolonged patients' lives by two to three months**.

On the other hand, **Edaravone** is a **reactive oxygen species scavenger** which has only been approved in certain countries for a few years. Its **pharmacological mechanism is uncertain**, but the drug is presumed to mitigate oxidative injury in motor neurons. The efficacy of the drug in treating ALS remains controversial. Hence, further studies are urgently needed for clinical validation of its efficacy.

The novel disease-modifying strategy shows promise to halt ALS progression. GDNF, which promotes the survival of motor neurons, has a short plasma life and fails to access the blood-brain barrier by itself. **Engrafting in the spinal cord**, the originally designed stem cells **differentiate into astrocytes**, and **secrete GDNF in the central nervous system**. The first human trial of this strategy was carried out to demonstrate safety in **18 patients with ALS**. The cells were unilaterally transplanted into the lumbar spinal cord to evaluate the safety after injection into the legs. The study was designed based on the fact that both legs lose motor function at a similar rate in ALS, with the untreated leg being the control.



While it was confirmed that there were **no negative effects on the muscle strength** of the treated leg compared to the control, there were some **limitations**. Due to the **small number of subjects**, more patients should be recruited to further evaluate the efficacy. Moreover, the majority of the participants were at **late-stages of ALS** during the time of treatment. Considering the neuroprotective nature of this strategy, it could be reasonable to expect better results if the strategy were to be employed at earlier stages. The problems brought by the surgical approach should also be addressed. **Benign growth of Schwann cells around the injection site** was revealed. This was likely attributed to the damage to the dorsal root entry zone during the surgery, followed by the proliferation of the damaged Schwann cells which could be stimulated by the GDNF release.

Some patients with grafts observed in the dorsal horn of the spinal cord reported having instances of pain as the **transplanted cells may have migrated to sensory areas**. Though the pain was eventually treated with medication, further trials should take the side effect into consideration in the context of the lethality of the disorder.

To optimise future clinical results, investigators aim to perform bilateral cell injections into both the brain and spinal cord targeting deeper into the ventral horn for more effective motor neuron protection. Overall, this **initial trial displayed encouraging clinical outcomes**, which provides the foundation for clinical studies on ALS in the future.

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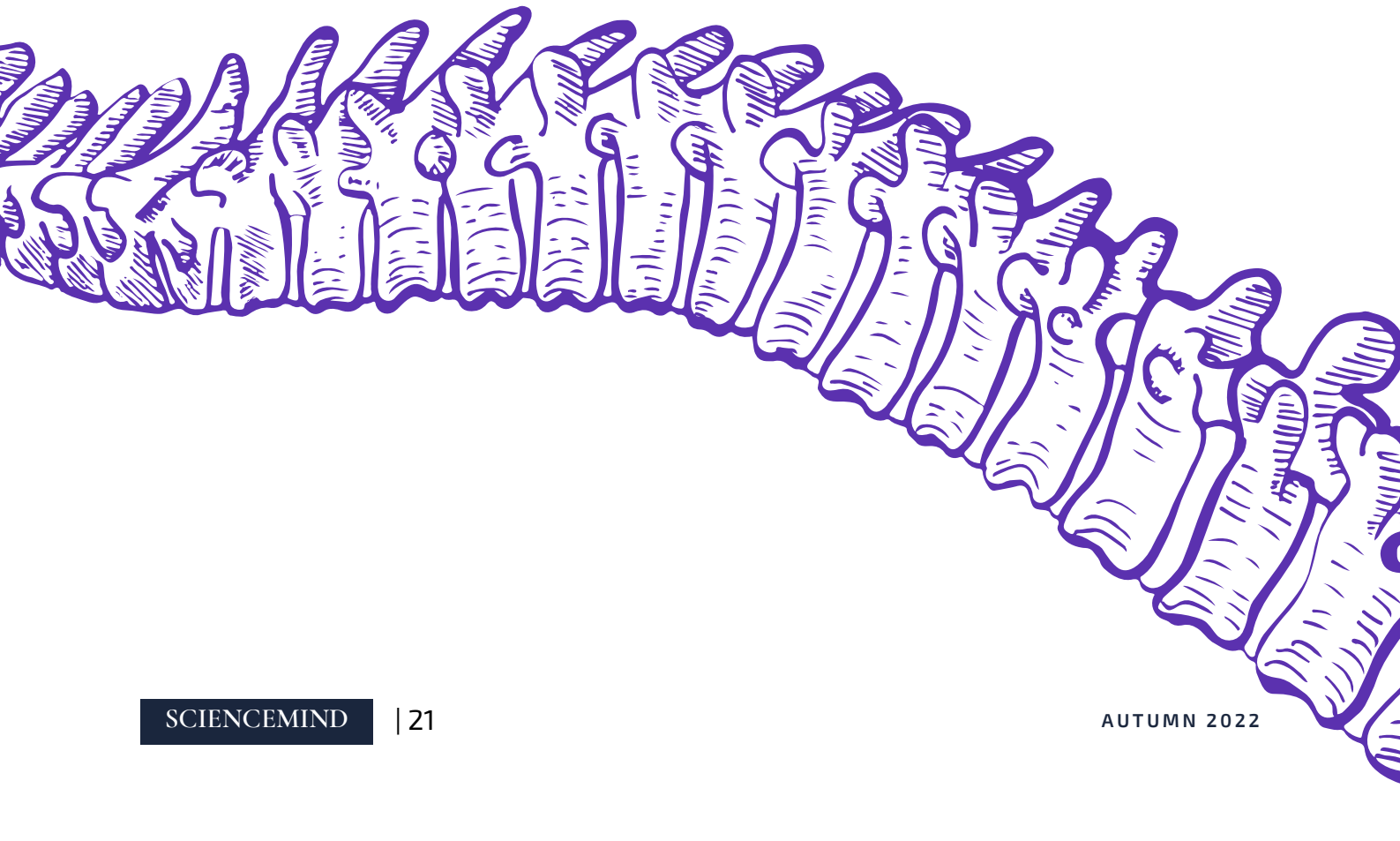

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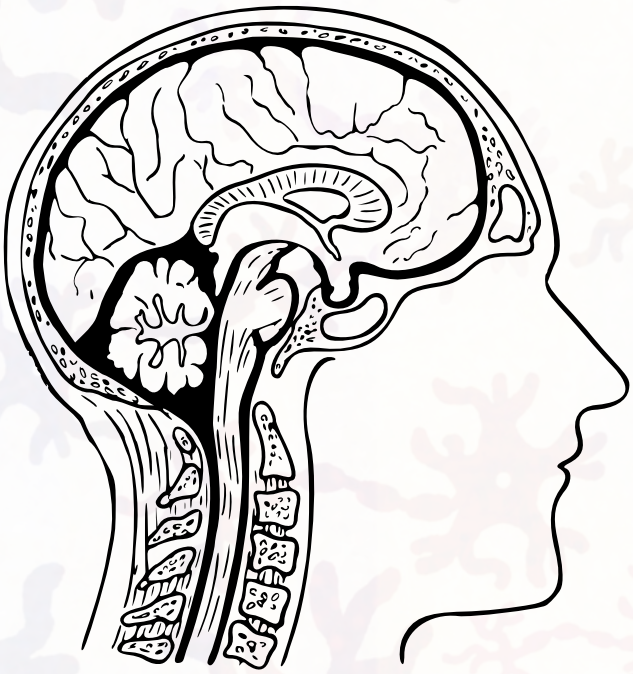
Glial brain tumours: Treatment barriers and breakthroughs

WRITTEN BY TULSI PATEL
EDITED BY PRACHI PURANIK
DESIGNED BY ALICE KOSMIDER

Mutations to a cell's **DNA** can lead to uncontrolled division, forming a large mass of cells, or a **tumour**. Over 130 forms of these types of tumours can occur in our **brain**, and over half of these are gliomas. These are named so as they develop from **glial cells**, the central nervous system's supporting cells.

Despite developments in surgical treatments that are combined with chemotherapy and radiotherapy, survival rates have only increased marginally. What makes brain tumour treatment so difficult is the inability to define tumour boundaries. It is vital that neurosurgeons keep surrounding brain tissue intact so any functioning deficits that occur from the surgery is minimised. **Gliomas** form by diffusing across cells and invading healthy brain tissues so they can grow, which is what makes this boundary hard to define.



How gliomas infiltrate the brain

Gliomas need space within the brain tissue to grow, and it does so by killing surrounding healthy tissue using an excessive release of the neurotransmitter, **glutamate**. Exorbitant amounts of glutamate in the brain fluid can have extremely **toxic** effects on the brain as it affects normal homeostatic processes. As gliomas kill healthy tissue, it needs to move into this newly created space and expand. They do so by changing cell volume via specialised transporters on gliomas that bring chloride ions into the cell from the surrounding fluids. When the ions move out of the gliomas, down the **concentration gradient**, to allow for an equilibrium state, it brings water out with it. This causes the cell to **shrink**. Now, it has the ability to move into tight spaces and take over space previously occupied by healthy tissue.

A hopeful future in brain tumour treatment

Recently, research has found the possibility of identifying these tumour boundaries. **Chlorotoxin (CTX)** is a peptide, derived from the **deathstalker scorpion**, and binds to the chloride channels in gliomas. Why is this a breakthrough? Because CTX can only bind to gliomas, and no other tissue in this body. In this way, using CTX can be a powerful tool for tumour **screening** and **diagnosis**. This was found when researchers combined CTX with **fluorescent molecules** to form a complex known as 'tumour paint', which allowed visualisation of the tumour boundaries (Veiseh et al, 2007), as demonstrated in Figure 1.

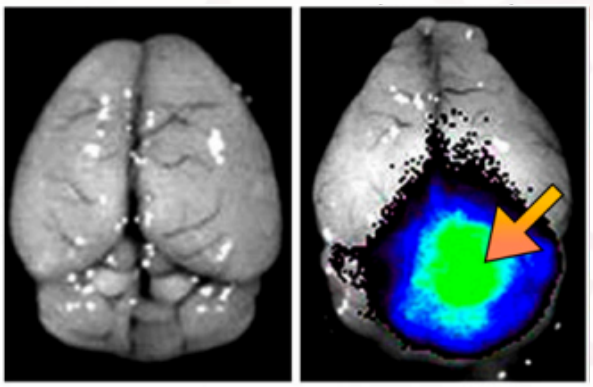
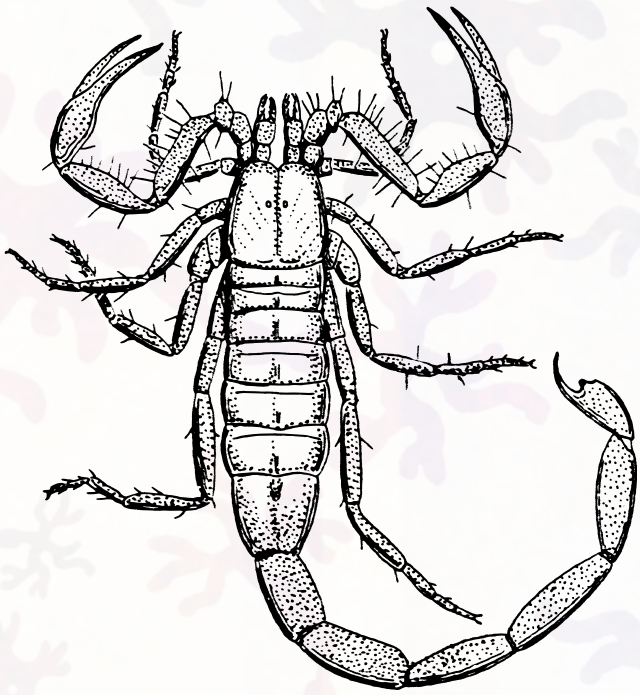


Figure 1: Scan of a healthy brain and a tumour brain injected with CTX (Cohen et al 2018).

In addition to CTX overcoming a huge barrier to brain tumour treatment, it can also be used to directly deliver **anti-tumour drugs** to the affected region. Once the tumour region is identified and surgery has been performed, radiotherapy/chemotherapy is needed. Here, CTX can be used to



deliver the therapeutic agent. When such a compound was developed, good tolerance and minimal radiation damage was seen in normal tissue. It was estimated by researchers that this treatment could double the patient's **life expectancy** (Mamelak et al, 2006).

This dramatic change in life expectancy has made CTX a breakthrough in scientific research. Since this, numerous studies have found the use of CTX in blocking tumour **malignancy**, and inducing cell death, however, more clinical studies are required to consider CTX as a viable treatment, but this is a promising start.

References

TREADING WATER

Lyme Neuroborreliosis - Neurological Manifestations of Lyme Disease

WRITTEN BY BEGONA PALENZUELA HERRERA
EDITED BY PRACHI PURANIK
DESIGNED BY ASHNA SURANA

Lyme Disease (LD) is a zoonotic vector-borne condition. The causative agent, ***Borrelia Burgdorferi* bacteria**, is transmitted to humans through the bite of an infected blacklegged tick (predominantly ***Ixodes scapularis***) (Vincent LoRe, Occi, & Macgregor, 2004). The **first sign of infection** is the appearance of the **erythema migrans (EM) rash**, which follows a target-like circular shape that develops in approximately 80% of the infected individuals (Steere, 2001). EM is often followed by a systematic inflammation in joints, muscles and in the central nervous system (Lochhead *et al.*, 2021) The purpose of this article is to review the neurological clinical manifestations of LD that often get misdiagnosed

Neurological Affection

When the causative agent, *Borrelia Burgdorferi* (predominantly) infects the peripheral and/or central nervous system, the neurological LD clinical manifestations begin to occur (Ford & Tufts, 2021). The inflammation primarily occurs in the **subarachnoid space** which houses cerebrospinal fluid (CSF) neurovascular structures and cisterns This inflammation leads to the clinical diagnosis of **meningitis** (Stupica *et al.*, 2014a pp.323–335). Thus, we can presume that LD could be a cause for the development of meningitis.

This is generally supported by **lymphocytic pleocytosis** in the CSF, to say a high concentration of lymphocytes in the patient's CSF (50-250 lymphocytes/mm3) (Xing et al., 2015).

Cranial nerves (distinctively the seventh cranial nerve), are also affected by Borellia Burgdorferi's infection. The interaction of the bacteria with the cranial nerves leads to **cranial neuropathy**, particularly face palsy, known as **Lyme-associated Facial Nerve Palsy (LAFP)**, caused by the inflammation of the mentioned nerves. This generally causes a unilateral facial palsy, meaning it only paralyses the muscles of one side of the afflicted's face. However, up to a quarter of the infected patients can develop bilateral LAFP. The affection to other cranial nerves (e.g., optic nerve) might occur but it is extremely rare (Marques et al., 2022).

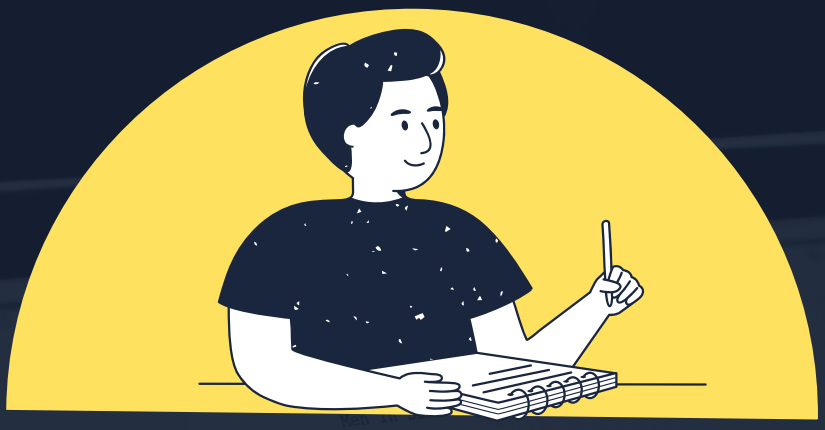
Individuals with Lyme neuroborreliosis are also afflicted with **painful radiculitis**, which describes the acute feeling of pinching and compression that radiates along the spinal nerve roots caused by inflammation at the root of the nerves connection to the spinal column (Hannoun & Gudin, 2017). This very disabling affliction is also often referred as **"lymphocytic meningoradiculitis"** because, as mentioned above it often comes accompanied by **meningitis and by lymphocytic pleocytosis** (Ryberg, 1984).

References

Correlation with Neuropsychiatric Disorders

Neuropsychiatric disorders **aetiological factors** are yet to be fully elucidated. It is known that most neuropsychiatric disorders are caused by a mix of environmental and genetic factors. Some environmental factors include the consumption of cannabis, or even infection by certain microbes such as by **protozoan *Toxoplasma gondii*** (Torrey & Yolken, 2003). The link between infection by certain microbes and the trigger of neuropsychiatric disorders is of increasing interest for researchers that have seen evidence and recognition that LD can also cause symptoms typical of neuropsychiatric disorders (Fallon & Nields, 1994).

Correlation between neuropsychiatric disorders and LD needs to be further studied as this might be a mere case of correlation and not causality.



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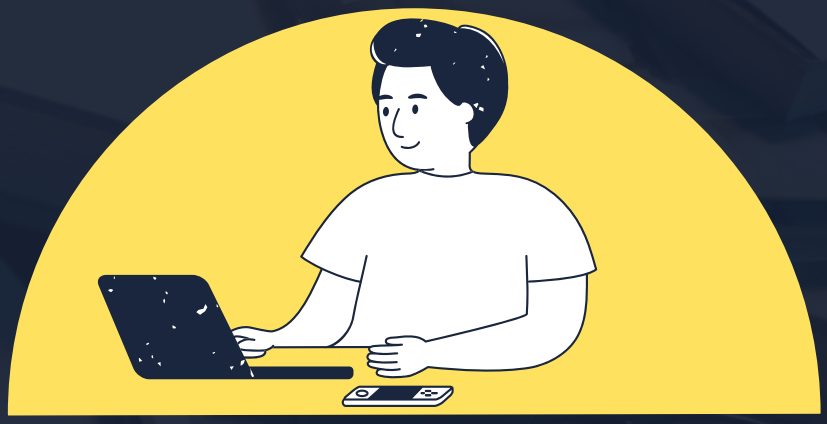

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