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Investigation of the Prevalence of the *mecA* Gene Across Staphylococcus Species Causing Resistance to Methicillin by Rustom Murgai Dubash

Introduction

Methicillin resistance is a major cause of hospital infections worldwide. Methicillin resistant *Staphylococcus aureus* (MRSA) is one such disease that has a high resistance to methicillin, due to the *mecA* gene [1]. This has become so prevalent, that out of 10 recognized *S. aureus* lineages, 8 of them had Gram - positive *mecA* strains [2]. Such MRSA strains are found commonly in hospitals worldwide, which cause a range of infections, some of which are life threatening, such as pneumonia, sepsis or simply mild irritations ranging from food poisoning to skin infections [3].

Methicillin was first introduced in 1959 as a substitute antibiotic for treating beta lactamase, and almost instantly after its discovery *S. aureus* became resistant due to the *mecA* gene. The *mecA* gene was first found in MRSA, but it then spread to many other *Staphylococcal* genus.

The problem arose because the *Staphylococcal* genus developed resistance to virtually all beta - lactam antibiotics [3]. Due to their low toxicity and high efficacy, beta - lactam antibiotics were among the most widely used [4]. The main reason behind resistance to beta - lactams, and therefore the creation of the *mecA* gene, is the constant exposure of *Staphylococci* to beta - lactams: in the soil near penicillin producing fungi, in animal farms where beta lactam antibiotics were used as food additives, and in the treatment of bacterial infections [5].

There are two main hypothesis about the spread of the *mecA* gene

The first theory, the clone hypothesis, which believes that *mecA* entered the *Staphylococcal aureus* species at one particular time and then resulted in the making of a single MRSA clone that spread all over the world [6].

The second hypothesis, which is based on the detection of *mecA* in *S. aureus* enzyme types, proposes that MRSA strains evolved a number of times by means of the horizontal transfer of *mecA*, into *S. aureus* strains [7]. However, further research has shown that the *mecA* gene, is located on a mobile genetic element known as staphylococcal cassette chromosome *mec*

(SCC*mec*), which then transfers into more strains, contributing to increasingly successful clones of *Staphylococcus aureus* [8].

My research will revolve primarily around the analysis of the proteins and the nucleotides concerning the *Staphylococcus aureus* and its relation to the *mecA* gene. This involves analysing the different sources of data and comparing their similarities and differences in the way data is presented. It also includes using BLAST to find similar sequences to better compare and classify the sequence of the *S. aureus* to already recognizable sequences [9]. Finally, this paper uses a number of techniques to find out more about the protein, ranging from its structure to its function.

Results

The five essential elements consisted of the locus, definition, accession number, version and origin. Both GenBank and DDBJ were very similar in these aspects, but the EMBL format had a number of differences. Where locus was given in GenBank, it was called the 'ID' in EMBL, although it consisted of exactly the same information. The definition was represented by 'DE' in the ENA, the accession number as 'AC', but the version was not specified in the EMBL format. The origin was represented by 'SQ' in EMBL, but a main difference between GenBank and the EMBL format is that the GenBank numbered on the right hand side, whereas the EMBL format was on the left hand side. Additionally, the GenBank numbered from 1 - 1981, and the ENA numbered from 60 - 2007.

I analyzed both the nucleotide sequence and the proteiTo compare the different databases for information about the *mecA* gene, we searched through the databases of the DDBJ (DNA Data Bank of Japan), the ENA (European Nucleotide Archive) and GenBank.

I searched for the "*S. aureus mecA"* gene by using the accession number "MW682923". My results were all performed with the gene sequence showing up in the FASTA file format; however, the format of the DDBJ, ENA and GenBank were all different in their means of presenting data.

There were a few key similarities between all three formats. Firstly, the gene sequence was identical in all three, as it had been done in a FASTA file format. However, the title of the Fasta file was different between GenBank and the ENA. The had its name written before the title ">ENA" like so, however GenBank did not include its name. Additionally, the FASTA files in

EMBL and DDBJ had the accession number, whereas GenBank did not (it only had version number).

Then I used BLAST to find similarities between different protein sequences. I used BLASTp for this. I got results with 100% accuracy and an E-value of 0 for all *Staphylococcal* groups. For nucleotides I used BLASTn to find organisms with similar sequences. My results for nucleotide sequences were 100 percent accuracy with an E-value of 0.00. All types of *Staphylococcus* were nearly identical to *Staphylococcus aureus*. So secondly, we excluded all *Staphylococcus* groups. The highest accuracy results were 100%, with an E-value of 0. These included 'Enterococcus hirae strain', 'Enterococcus faecalis' and 'Enterococcus faecium'. Another notable result is accession no. 'KY701739', which also has an E-value of 0, but a 99.90 percent accuracy. Finally, I analyzed proteins by using BLAST. I found many similar results: E-values of 0, and percentages of accuracy of 99.85, 99.70 and 99.70 for accession numbers 'HIS18600', 'ASN64787' and 'NZD73189' respectively.

To find out more about the related proteins and their functions, I started with PDB (Protein Data Bank). It is classified as a penicillin binding protein, which explains why it falls into the category of beta - lactams. Additionally, there is also a high number of motifs present, and the PubMed extract provides further information as to how the resistance of the MRSA works to stop biosynthesis of their peptidoglycan cell wall. To find out more, I searched the accession number in UniProt, however, there were no search results as to what the function of the protein was.

We searched for the sequence on Pfam, and found 3 domains belonging to the Transpeptidase, PBP Dimer and MecA N families. These results were intriguing, since both the Transpeptidase and PBP Dimer families were both penicillin - binding proteins.To verify these results, I went onto Interpro to check my conclusions. They matched up exactly with those from Pfam, ensuring that the data was correct.

Lastly, I used the tool Phobius to try to identify the protein signatures of the particular sequence [10]. This again was very revealing: the protein resides entirely in the transmembrane region, neither in the cell, nor outside it. So the protein clearly plays an important function by acting as a transportation channel or a signal receptor. Clearly the protein plays a central role in antibiotic resistance.

Discussion

These findings help contribute to the understanding we have of the *mecA* gene in the *Staphylococcal* genus, in particular the *Staphylococcus aureus*. The results of the analysis of the different databases helped clarify the way the data was presented, and how to analyze and better interpret the results. It helps to know which resource has the right data for your research, and in this particular case, the GenBank format worked the best for retrieving necessary data. However, the DDBJ and EMBL formats should not be discounted as they too had important information.

The BLAST results helped confirm a lot of results from previous research. For one, the percentage accuracy was 100% and the E-value was 0 for nearly all the *Staphylococcal* genus, which confirms that the *mecA* gene is not only present in *S. aureus,* but also in other *Staphylococcal* genus. This further displays how big a problem the antibiotic resistance is to beta - lactam antibiotics, as it spreads from bacteria to bacteria until antibiotics like methicillin become practically ineffective.

The BLAST results support another hypothesis that antibiotic resistance to beta - lactams is not just spreading to different *Staphylococcal* genus, but also to other bacteria. The results specifically show high percentages and low E-value that essentially confirms that the particular gene or protein is present.

This research also provided insight into how beta - lactams work: by bio synthesizing the peptidoglycan cell wall. This was shown by the Protein Data Bank results. They also helped explain why the protein is relevant to beta - lactams: it is classified as penicillin binding.

However, it is interesting that there was no result shown on UniProt, which is a very large secondary database used mainly for identifying a protein's function. In this case, it did not have any information regarding the protein's function, indicating that there is still a lot more to be learnt about the protein and its role in antibiotic resistance. In fact, this is doubly interesting considering that the protein in question is that the protein comes up in the transmembrane region on Phobius, as proteins that are in the cell membrane play an very important role for the cell.

Methods

For my research, all of my methods were online. Firstly, I used the different search and download functions of the databases in the INSDC (GenBank, ENA and DDBJ). Then I used the different FASTA files to compare formats and check for variation in the information provided.

To compare the sequence of the protein to other known sequences, I used BLASTp and to compare the nucleotide sequences I used BLASTn.

Finally, I used PDB to get information on the structure of the protein, and UniProt to understand its function. I utilized Pfam and Interpro to check for conserved protein domains, and Phobius helped me look for distinct protein signatures.

Conclusion

My research rotated around using different tools to find information to help us understand how the *mecA* gene contributes to antibiotic resistance over a spectrum, particularly *Staphylococcal* genus, but more broadly over beta - lactams and more specifically on *S. aureus* (MRSA). These tools included the INSDC databases, BLAST analysis and 5 main secondary databases (PDB, UniProt, Pfam, Interpro, and Phobius).

The results from these investigations yielded important results relevant to previous studies, particularly related to the protein found in the cell membrane and on how resistance to antibiotics like methicillin can transfer between bacteria of the same species and even some from different species. Additional results included insights into the structure of the protein or variations in sequencing format.

However, future research will be needed to truly find a way to solve the growing issue of antibiotic resistance to methicillin, and all beta - lactams. I would say that an important piece of information to clarify would be that of the function of the protein, and also to understand how the antibiotic resistance carried by the *mecA* gene is transferred to other species, especially those of different genus.

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Race and Sex Disparities Impacting the Spread of COVID-19 in the United States by Angelina Hui

Abstract

SARS-CoV-2, the causative agent of COVID-19, is a member of the coronavirus family. Since the first outbreak of COVID-19 in December 2019 in China, epidemiological data have suggested that factors such as co-morbidities, sex, race, and other factors contribute to disease susceptibility and severity. Males are reported to have a 65% higher chance of dying from COVID-19 than females. In addition, 15% more males are admitted into intensive care units. The difference between the severities of the two sexes can be in part related to the X chromosome. Regulatory genes that impact the function of immune cells are abundant in X-chromosomes, such as toll-like receptor genes, which are critical to fighting the viral antigens. Because females at birth have two sets of X chromosomes, their body naturally expresses more of these immune-regulatory genes which will therefore impact the function of the immune response. Other factors such as hormones and behavioral differences may also contribute to the COVID-19 disease severity gap between males and females. Finally, data has also shown a disproportionate impact of COVID-19 in minorities, especially in low-income communities that lack access to healthcare. Socioeconomics, biological and immune differences, and lack of racial equity all have a role in the deadly spread of COVID-19 in minority populations. Here, we review current data exploring why certain demographics are more severely impacted by COVID-19 from a biological and socioeconomic standpoint.

Introduction

On December 31, 2019, Wuhan Municipal Heath Commission in China, revealed that a novel coronavirus, later named SARS-CoV-2 by the World Health Organization (WHO), was causing cases of pneumonia in Wuhan, Hubei Province. By January 14, 2020, Thailand had officially reported its first case of infection with SARS-CoV-2, now dubbed “COVID-19”. This mystery virus spread quickly, deeply concerning the WHO, whom on March 11, 2020, declared COVID-19 a pandemic (WHO, 2020).

SARS-CoV-2 is a new coronavirus that targets the respiratory system and uses its RNA sequence to replicate itself within a host. It is defined as a zoonotic coronavirus, meaning it replicates in multiple animal reservoirs and humans, with the ability to cross species barriers.

COVID-19 is spread through respiratory droplets caused by sneezing or coughing. Once the pathogen enters the lungs, the virus uses its spike proteins on the surface to bind its corresponding receptor to gain access into the host cells. Its primary receptor is the angiotensin-converting enzyme 2 (ACE2) receptor found on the cell membrane (**Figure 1**). Once the virus is inside the host cell, it hijacks its organelles to reproduce itself to infect more host cells (Chowdhury, et al., 2020). SARS-CoV-2 bears similarity with SARS-CoV-1, Middle Eastern Respiratory Syndrome (MERS), and endemic coronaviruses. SARS-CoV-1 and MERS were responsible for causing pandemics in 2003 and 2012, respectively, causing 10,984 cases in total (Zhang, et al., 2021; Chan-Yeung, et al., 2003). Though the endemic coronaviruses we see today and the ones seen years ago have some sequence similarities, pre-existing immunity is not enough to confer protection against the novel SARS-CoV-2 virus. For this reason, the spread of COVID-19 has become one of the deadliest pandemics in modern history.

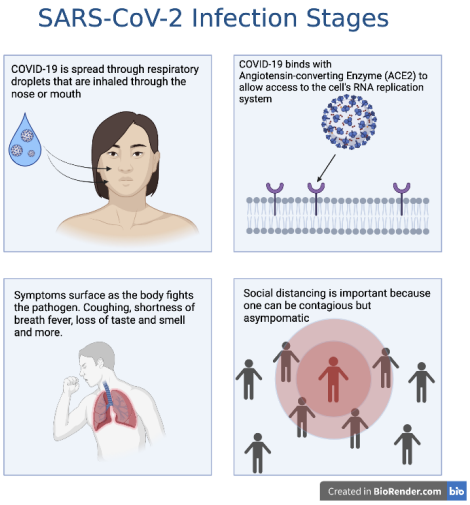

Figure 1. Infection stages of SARS-CoV-2 (COVID-19) from initial infection to transmission. [A] shows a blue droplet containing coronaviruses to represent a respiratory droplet infected with COVID-19. The black arrows indicate that the droplets enter a new host through the nose or mouth. [B] depicts the coronavirus now binding to a purple y-shaped receptor that is located on top of a lipid bilayer membrane. This represents COVID-19 binding to an ACE2 protein that is located on a host's cell membrane. [C] shows highlighted lungs and a man coughing to represent the symptoms of COVID-19. [D] shows a red figure that represents someone who is infected, and the red circles represents how close someone can be to become infected. Any grey figure that is within the red circles are now infected as well (WHO - Coronavirus disease (COVID-19)). Created with BioRender.com

Several studies have revealed that the male sex is more likely to exhibit severe symptoms and mortality compared to females (Shim, et al., 2020). Factors such as naturally-derived genes, hormones, immune responses, harmful habits such as smoking, mentality about the pandemic, and hygiene may contribute to the differences in severity between males and females.

Lower-income families and minorities have also seen higher rates of infection and deaths in their communities. Data from the Centers for Disease Control and Prevention (`) in the United States has shown wildly disproportionate COVID-19 infections within Black communities. Compared to White, non-Hispanic persons, Black or African Americans are 2.6 times more likely to become hospitalized (CDC - Risk for COVID-19 Infection, Hospitalization, and Death by Race/Ethnicity, 2021). These alarming statistics raise questions about inequities in healthcare. Finally, some studies have shown biological differences between races that could contribute to disproportionate infection rates, though the data are limited.

In this review, we summarize the potential risk factors of individual groups and communities, focusing on genetics, hormones, social behaviors, and socioeconomic factors.

Sex Disparities in COVID-19

Data collected on COVID-19 infection and mortality rates have shown a disproportionate number of males contracting and dying of the pathogen. The male mortality rate in the United States is higher than females with the exception of the 85 years and older age group (**Figure 2**). Moreover, 60% of global deaths from COVID-19 are from men (Gebhard, et al., 2020; CDC Covid Data Tracker, 2020). The same findings have been reported in previous coronavirus outbreaks such as SARS-CoV-1 and MERS. Scientists point to gene expression, levels of ACE2 expression, and hormones as some of the potential root causes.

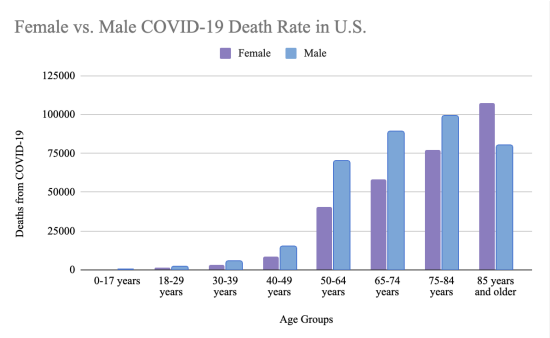

Figure 2. Difference in mortality rates between men and women in different age groups with COVID-19. The purple bars represent Female population, and the blue bars represent the Male population. Until the age group older than 85, males have a significantly higher mortality rate than females [Data sourced from CDC Covid Data Tracker (Accessed on 11/23/21)].

Genes involved in both innate and adaptive immune responses are abundant in the X chromosome. This in turn gives biological females a heightened immune response, with the higher phagocytic activity of neutrophils and macrophages, and more efficient antigen-presenting cells (Spitzer, 1999; Weinstein, et al., 1984). From the womb to adulthood, females seem to have better health outcomes than males (Libert, et al., 2010).

ACE2 is a regulator for the renin-angiotensin system but is also a receptor for SARS-CoV-2 to invade a host cell. ACE2 can be found in the lungs, heart, kidney, endothelium, and intestines; some comorbidities, however, can lead to increased levels of ACE2 expression, worsening COVID-19 disease severity. It has also been suggested that ACE2 levels increase with age, which could be why older individuals are more prone to more severe diseases (Chen, Li, 2020).

Sex disparities seen in the COVID-19 pandemic can also be explained by the expression of sex hormones. Androgens upregulate transmembrane serine protease 2 which is one of the primary ways SARS-CoV-2 enters a host cell (Hoffmann, et al., 2020). Androgen is often seen at a higher concentration within the male population which can explain the severity of COVID-19 within males. Additionally, testosterone along with progesterone has been shown to have immunosuppressant effects, which could impact immune responses that control SARS-CoV-2 infection. Below, we summarize various studies that highlight differences between men and women that impact COVID-19 disease susceptibility and severity.

One of the greatest noted differences between men and women impacting COVID-19 disease susceptibility and severity is due to immune systems. In a study at the Wuhan Union Hospital, Tongji Medical Center of Huazhong University of Science and Technology, the concentration of 331 COVID-19 patients' SARS-CoV-2 IgG antibodies was analyzed (Zeng, et al., 2020). The study consisted of 127 males and 204 females who were divided into four groups based on their infection severity (mild (22), general (87), severe (22), and recovering (200)). The average ages within the 'mild' cohort ranged from low to mid-40s; average ages within the 'general' cohort mid to high 40s; average ages within the 'severe' cohort high 50s to low 60s. In the 'recovering' cohort, the average ages were nearly the same as the 'mild' and 'general' groups. Males only accounted for 35.5% of recovering patients as opposed to 64.5% of recovering female patients (Zeng, et al., 2020). When observations were completed, it was found that in the severe status, antibodies were higher in females compared to males. While antibodies

of female patients were recorded as more than 100 AU/mL, those of most male patients were lower than 100 AU/mL. The trend of higher concentrations of antibodies in females remains 2 to 4 weeks after disease onset; after 4 weeks, the difference in concentrations is not distinguishable. Together, these data show that females have a stronger IgG antibody production at the early stages of infection compared to male patients (Zeng et al., 2020).

Another study done in Yale New Haven Hospital between March 18 and May 9, 2020, used biospecimens of blood, nasopharyngeal swabs, saliva, urine, and stool to analyze the sex differences in immune phenotypes in males and females (Takahashi, et al., 2020). Within the study, there are two cohorts, A and B. Cohort A consists of 39 patients, 17 men, and 22 women. Male and female patients in this cohort were matched regarding age, body mass index, and days from the symptom onset. Cohort B includes all patient samples from Cohort A with an additional 59 patients. After analyzing 71 cytokines and chemokines, it was found that there were higher interferon (IFN) a2 levels in female patients than male patients in Cohort B. Additionally, interleukin (IL)-8 and IL-18 were considerably higher in males than females in Cohort A. CCL5 was significantly elevated in male patients compared to female patients over the disease course. When looking at monocyte differences, male patients in Cohort B had drastically lower T cells in both count and proportion to live cells compared to female patients. Male patients also had higher levels of $CD14^{lo}CD16^{+}$ non-classical monocytes compared to controls and female patients. After further examining T cell phenotypes in COVID-19 patients, levels of CD38, HLA-DR-positive activated T cells, PD-1, and TIM-3-positive were all found to be more abundant within female patients compared to their male counterparts (Takahashi, et al., 2020).

Finally, differences in ACE2 expression also play a large role in sex disparities in COVID-19. A study was done by BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) explored the plasma concentration of ACE2 in two large, independent cohorts according to the use of the renin-angiotensin-aldosterone system (RAAS) to conclude whether RAAS inhibitors increase plasma ACE2 concentrations (Sama, et al., 2020). Observations were over 11 European countries with 1485 men and 537 women with heart failure. The mean ages for the men and women were 69 and 75 years old, respectively. The two cohorts, index and validation, were similar in most the same, however, the index cohort consisted of patients who had a left ventricular ejection fraction greater than 400 ng/L or N-terminal proBNP greater than 2000 ng/L. In both index and validation cohorts, men were observed to have higher levels of

ACE2 compared to women. Males in both cohorts were more likely to experience atrial fibrillation, a higher heart rate, and lower systolic blood pressure. Meanwhile, in the validation cohort, males also had a higher chance of encountering diabetes. Within the group that did not receive RAAS inhibitors, men were predominant in the uppermost quartile of ACE2 expression. In 9 out of 11 countries, ACE2 concentrations were higher in men than in women (Sama, et al., 2020). This contributes to the gaps between male and female COVID-19 disease severity.

Social Differences

Men are observed to be more at risk for contracting COVID-19 for several reasons other than biological differences. Social behaviors including physical distancing, wearing masks, hand washing, and personal habits such as smoking and drinking alcohol have been reported to be higher in men than women (Shim, et al., 2020). These social behaviors greatly influence COVID-19 disease susceptibility and can compromise the immune system. Since respiratory droplets can spread more than 6 feet when sneezing or coughing, it is important to keep as much distance from another individual when able to.

Since COVID-19 is primarily a respiratory disease, long-term habits like smoking and frequent drinking can increase the severity of infection. Prolonged cigarette use can cause chronic obstructive pulmonary disease (Zhao, et al., 2020). Because males have higher rates of smoking and drinking, they are in turn more likely to have suppressed function of the lungs and weakened immune systems (Chanana, et al., 2020). However, it is important to note that only a fraction of the male population meets these criteria, and thus the overall differences in susceptibility and severity at the population level are likely minor.

Racial Disparities in COVID-19

In addition to sex differences, racial differences also impact COVID-19 disease susceptibility and severity. To date, some studies have suggested that there are differences in gene expression and immune function between Black and White patients that may underlie racial disparities in COVID-19. A study done at the Nottingham University Hospitals led by Ana M. Valdes in the United Kingdom (UK) identified that seropositivity was higher in Black participants independent of age, sex, and economic standing (Valdes, et al., 2021). In an observational cohort study, 1364 frontline healthcare workers (HCW) at five UK hospitals were

studied. Of the 1364 HCW, 73.5% were white, 4.2% Black, 9.4% South Asian, 5.7% East Asian, 6.2% other/mixed. From March 20 to July 10, 2020, HCW were questioned about symptoms and underwent antibody testing. 24.8% of participants reported symptoms while the rest had atypical symptoms or were overall asymptomatic. From the study, it can be concluded that the rates of infection were higher in Black HCWs (42%), however, there was no significant relationship between seropositivity and other ethnicities compared to white HCWs. Additionally, there were no associations of seropositivity with age, body mass index, sex, Index of Multiple Deprivation, and use of personal protective equipment outside of intensive therapy units. Even after considering other confounding variables, the relationship between the Black race and the increased risk of infection remained significant. It was hypothesized that these results could possibly be from individuals from different ethnic groups responding differently when confronted with an infection. For example, an individual from one ethnic group may have a different immune response to another individual from another at the same level of exposure. Though this study was primarily done on HCWs, it does not change their responses to COVID-19 and should reflect the general population. More studies are required to better understand the biological differences at play impacting racial disparities in COVID-19 infection, and how many potential differences may intersect with socioeconomic factors.

Another study conducted by Yu Zhao and colleagues analyzed 43,134 cells derived from normal lung tissue of 8 adult donors for single-cell RNA-Seq analysis (Zhao, et al., 2020). They found significantly higher ACE2 expression within Asian males, which may impact the susceptibility of Asian individuals to COVID-19. However, more research must be done on increased numbers of human participants to confirm these results.

Socioeconomic Differences

Finally, socioeconomic differences have a major impact on the disproportionate spread of COVID-19 within certain racial communities. Recent data has shown that there is a disproportionate impact of COVID-19 on minorities and lower-income families (Garg, et al., 2020). The ratio of racial/ethnic cases, hospitalizations, and deaths is often much higher compared to White, non-Hispanic individuals (**Figure 3**). Below, we explore potential socioeconomic factors that impact racial disparities in COVID-19.

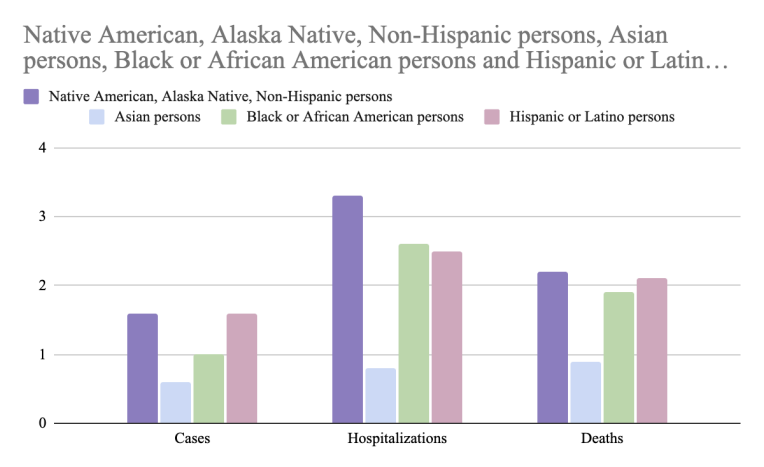

Figure 3. This figure compiled by the United States Centers for Disease Control and Prevention shows the ratios of racial and ethnic minorities rate of cases, hospitalization and death compared to White, Non-Hispanic persons. [Data sourced from CDC - Hospitalization and Death by Race/Ethnicity (Accessed on 11/22/21)]

Redlining is a significant factor in the overwhelming spread of infectious diseases within communities. Redlining is a historical US government policy that originated in the 1930s (Li, Yuan, 2021). The Home Owners' Loan Corporation (HOLC) assessed and provided grades to residential neighborhoods on their "mortgage security". Neighborhoods that were deemed undesirable to lenders were outlined on a map in red and received a "D". Though these assessments on neighborhoods were based on class, occupation of residents, and building quality, it was common for HOLC to redline communities with predominantly African American and immigrant residents, assuming the share of immigrant and black families lowered the values of homes. Because of these policies, many neighborhoods with predominantly Black or ethnic minorities lack investments and loans that have caused crowded housing, poor housing quality, lower quality local government services, lack of recreational facilities, and healthy food establishments. Though redlining became illegal after the Fair Housing Act of 1968, the act did not undo the long-lasting effects of redlining. Because these communities are targeted for unhealthy products including fast foods, cigarettes, and alcohol, residents have a higher rate of chronic medical conditions. These medical conditions are also risk factors for COVID-19 that increase the chance of having a severe infection and possibly death. For example, this can be seen in southeast Brooklyn, New York, which is predominantly Black and has almost two times the death rate of its neighboring white community in East Harlem (Li, Yuan, 2021).

As the pandemic continues on, African American and Latinx workers are the least likely groups able to work from home. In New York, once the epicenter of the COVID-19 disease, 75% of frontline workers were people of color, which significantly increased their chances of contracting COVID-19. This is on top of 45% of essential workers in the foodservice industry that does not have access to paid sick leave (New York City Comptroller, 2020). According to a ColorLines study from 2019, 9.7% of Black Americans are uninsured which is nearly double the uninsured rate of White Americans (5.4%). This study also found that 17.8% of Latinx individuals are uninsured which is immense given that 18% of the US population is Hispanic or Latinx (Saxon, 2020).

Conclusions

During the COVID-19 pandemic, there has been a clear infection bias in men within most countries. The differences between the immune systems of males and females could be one of the biggest factors. Females have a more robust immune response to infections, which could be associated with the abundant immune genes on the X chromosome. The immunosuppressant traits of testosterone, androgen, and progesterone could be a key element as to why we see males have a higher severity of infection and mortality rate. Since ACE2 is one of the primary ways SARS-CoV-2 uses to gain access to the host cell organelles, males are more susceptible to infection and disease severity due to their natural higher expression of ACE2. Social differences are also a factor that one needs to consider as men participate in drinking and smoking more than women. The suppressed function of the lungs and immune system greatly affects how the body's immune system fights pathogens like SARS-CoV-2. Social differences are a critical part in determining how your body reacts to a pathogen, but it does not affect your immune system as much as how your natural immune system exerts.

Social and Biological Differences Between Races

Not only do men and women have gaps between severity and mortality but so do racial minorities and low-income families. Lack of access to healthcare, overcrowding of homes, and 75% of frontline workers being people of color, all contribute heavily to the susceptibility and severity of COVID-19. Biologically, there has been little research done to identify whether there is anything genetically different between races and ethnicities. A study found that ACE2

expression is higher in Asian men, however, more studies will need to be conducted to conclude a significant difference. It may be still relatively early in the pandemic, so more research should be more abundant later in the upcoming year. Ultimately, identifying and understanding these knowledge gaps is critical for slowing the spread of COVID-19 and ending this deadly pandemic.

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The Effect of Common Cancer Treatments on the Developing Brain: A Review by Maryam M. Shabar

Abstract

The purpose of this review is to incorporate information from various evidence-based sources that examine the neurobiological effect of cancer treatments on the developing pediatric brain. We first investigate the topic from an anatomical standpoint, where two major brain regions are of interest: amygdala-prefrontal cortex (PFC) and the hippocampus. Next, we discuss the normal developmental trajectories of both regions and the potential neurotoxic consequences of cancer treatment. Then, we examine aversive learning and the decreased ability for fear extinction in the context of cancer-induced posttraumatic stress/posttraumatic stress disorder (PTSS/PTSD). We then provide three studies, each focusing on one treatment: radiation therapy, chemotherapy, and surgery. Finally, we derive scientific perspectives from several authors that provide considerations, interventions, and ways to minimize the neurotoxic outcomes of these cancer therapies.

Introduction

Surgery, radiation therapy, and chemotherapy are three of the most employed cancer treatments for pediatric cancer. While these treatments frequently yield successful results, effectively destroying rapidly proliferating cancer cells, this review assesses the psychological and physiological aftermath of these treatments on the pediatric brain and its normal development processes. Humans have one of the slowest brain development timelines of all species, with full brain maturation occurring in an individual's 20s (Johnson et al.). Thus, cancer diagnoses and subsequent treatment may be more likely to coincide with critical stages of brain development, which poses a threat to the developmental trajectory of the pediatric brain (see Fig. 1) (Jones and Pattwell 100657).

To better understand the effects of these treatments on the developing brain, I will provide context by underscoring two critical categories of normal development in the brain: amygdala prefrontal cortical connections and hippocampal connections.

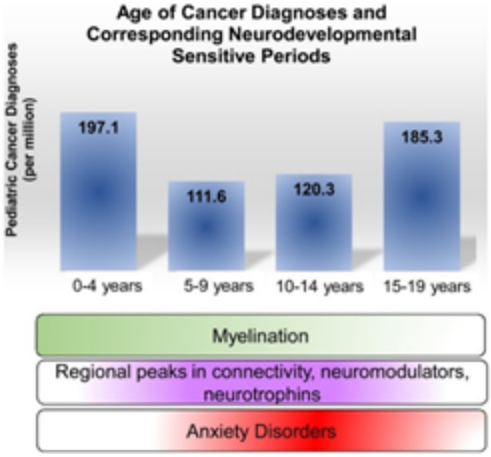

Figure 1. Pediatric cancer diagnoses coincide with normal developmental periods (myelination, peaks in connectivity, neuromodulators, and neurotrophins, and anxiety disorders)

Figure from "Jones, Rebecca M., and Siobhan S. Pattwell. "Future Considerations for Pediatric Cancer Survivorship: Translational Perspectives from Developmental Neuroscience." Developmental Cognitive Neuroscience, vol. 38, 2019, p. 100657., https://doi.org/10.1016/j.dcn.2019.100657."

Amygdala Prefrontal Connections

Consequences of altered amygdala-prefrontal cortex (PFC) connectivity can cause dysregulated PFC control over the amygdala. Given the amygdala's salient involvement in fear, this dysregulation can result in the pathogenesis of debilitating anxiety and fear disorders (Liu et al. 2221). The amygdala is most famous for its prominent role in eliciting fear response, such as "fight or flight." But this brain region's functions also include memory; namely, emotional fear memories (Sukel). A principal characteristic of the brain is its interrelatedness; the prefrontal cortex is highly involved in executive functions, but most importantly for the understanding of the amygdala-PFC region is the regulation of the amygdala.

Adolescence is a time during which the amygdala shows functional and structural development and is vulnerable to external stressors such as cancer treatment. In early childhood, a brain undergoing normal development will exhibit immature connections between the PFC and the amygdala (Gee et al. 15638-43). These connections occur gradually, as seen in rodents whose

amygdala-PFC connections develop throughout adolescence (Tottenham, Nim, and Galván. 217-27). From an anatomical perspective, the amygdala experiences volumetric changes which correlate with pubertal developments (Tottenham, Nim, and Galván. 217-27) and connections within the PFC-amygdala circuit continue to mature (Gogtay et al.).

To strategically analyze the effects of cancer treatment on the developing brain, I will apply Marusak et al.'s classification of cancer experience as a potentially traumatic event for pediatric patients. First, however, it is essential to note that a significant percentage of pediatric cancer survivors emerge psychologically well and report that cancer experience made them more resilient (Marusak et al.). Still, an overwhelming body of research indicates a risk for neurobiological changes resulting from the cancer experience, even for those who come out psychologically well. According to Marusak and colleagues, structural and functional changes in the brain correlated with trauma-related consequences, such as PTSS/PTSD (post-traumatic stress syndrome/post-traumatic stress disorder), implicate brain regions involved in fear processing, threat detection, and the inhibition of inappropriate fear response. In PTSS/PTSD, the fear circuitry of the brain [amygdala, ventromedial prefrontal and adjacent ventral anterior cingulate cortex (vmPFC/vACC), hippocampus, and the dorsal anterior cingulate cortex (dACC)] are most relevant. Anxiety disorders like PTSS/PTSD are characterized by the abiding fear of an environmental threat, even after the threat no longer exists (Pattwell et al. 16318–23). Cues that are associated with the fear memory may trigger inappropriate responses, such as episodes of intense panic and/or vivid flashbacks of the traumatic experience. From a cancer treatment perspective, pediatric patients could potentially develop triggers that are associated with frightening aspects of treatment.

In youth who experienced trauma, a more hyperactive amygdala was observed in comparison to healthy controls. Since the amygdala is responsible for fear response, this observation indicates that trauma can alter the amygdala's functionality, betweenness centrality (the level of influence a neural network has over the communication of surrounding neural pathways), and development (Marusak et al.). A disruption in the amygdala's development triggers developmental interruptions in other brain regions, which leaves the brain vulnerable to PTSS/PTSD. One study utilizes MRI technology to examine the effects of cancer-induced PTSS/PTSD in children. The study revealed increased amygdala centrality in the brain; and a higher probability of re-experiencing PTSS/PTSD (see Fig. 2) (Marusak et al.).

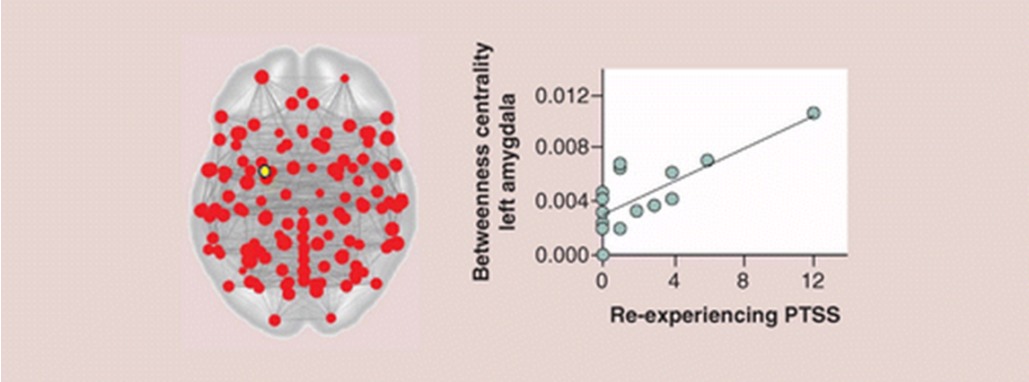

Figure 2. The amygdala (yellow) is represented within the larger brain network. The graph models a positive correlation between amygdala centrality and re-experiencing PTSS.

Figure from "Marusak, Hilary A, et al. "Pediatric Cancer, Posttraumatic Stress and Fear-Related Neural Circuitry." International Journal of Hematologic Oncology, vol. 8, no. 2, 2019, https://doi.org/10.2217/ijh-2019-0002."

Regarding the amygdala-prefrontal connections discussed earlier, studies have revealed altered connectivity between these vital regions in trauma-exposed youth (Jones and Pattwell 100657). More specifically, the connections between the amygdala and the vmPFC/vACC, which are essential for emotion regulation. In trauma-exposed adults and youth, a smaller vmPFC/vACC volume is reported; this structural alteration is associated with re-experiencing PTSS (Marusak et al.). Furthermore, the vmPFC is crucially involved in fear extinction, and findings revealed that patients re-experiencing PTSS have issues with fear extinction. Thus, for pediatric cancer survivors, treatment related PTSS/PTSD can inflict detrimental outcomes on the normal development of the amygdala and its prefrontal connections that safeguard the brain from psychopathologic manifestations.

Hippocampus Connections

The foundation of this review is that the brain continues maturing until approximately 21 years of age (see Fig. 3). The hippocampus is a critical brain region that experiences rapid cell

proliferation during development; thus, some pediatric cancer treatments that target rapidly proliferating cells, like chemotherapy or radiation therapy can also affect healthy cell proliferation in the hippocampus (Dietrich et al. 224-32). During normal brain maturation, processes like myelination, synaptic pruning, and changes in cell proliferation and apoptosis take place.

The brain consists of two forms of tissue: white matter and grey matter. Grey matter consists of nerve cell bodies and unmyelinated axons. White matter is composed of myelinated axons; the myelination of axons is a critical process in hippocampal development where neurons are coated with a protective sheath. Therefore, myelination occurs during development, seeing as there is an increase in white matter and a decrease in grey matter as the brain matures.

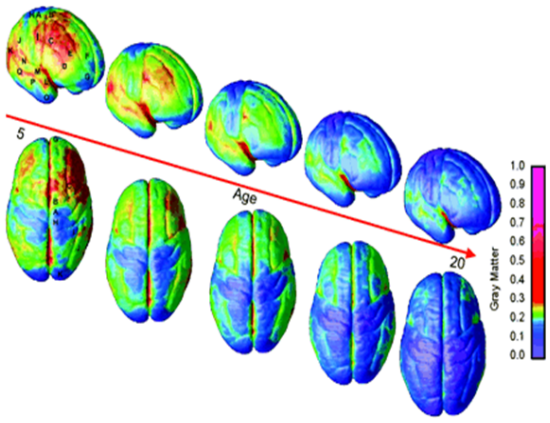

Figure 3. In a longitudinal study, Gogtay et al. scanned children between ages 4 and 21, every two years. The color bar indicates grey matter volume in the brain. As the brain matures, there is a nonlinear decrease in grey matter and a linear increase in white matter.

Figure from "Gogtay, Nitin., et al. "Dynamic Mapping of Human Cortical Development during Childhood through Early Adulthood." Proceedings of the National Academy of Sciences of the United States of America, U.S. National Library of Medicine, https://pubmed.ncbi.nlm.nih.gov/15148381/."

The normal development of a myelin sheath is instrumental in ensuring effective and smooth electrical cell signaling in the brain (Weickenmeier et al. 119-24). Further, a study by

Weickenmeier et al. suggests that myelination is also involved in the provision of the stable microstructural network that supports white matter.

Alterations in white matter activity due to coinciding cancer treatments may alter the myelination process. Disruptions in myelination could lead to abnormal conduction in electrical cell signaling, slower processing speed, and decreased accuracy of transmitted impulses. The myelination process is of the essence, as it is responsible for axonal activity and many complex brain processes (Gould et al.). The myelination process is conducive to hippocampal development seen in childhood and adolescence (Jones and Pattwell. 100657). Ergo, the hippocampus may be particularly susceptible to the neurotoxic effects of cancer treatments. Another vital hippocampus development process that is vulnerable to neurotoxicity is synaptic pruning, which is involved in connectivity and the strengthening of neuronal connections. To describe the formation of neural connections, famed psychologist Dr. Donald Hebb said, "neurons that fire together, wire together." Synaptic pruning is highly contributory to the developing neuronal wiring of the pediatric brain. It refers to how the brain eliminates extra, unneeded synapses and strengthens or wires connections that serve critical functions. This targeted elimination of synapses is essential for brain plasticity and adaptivity (Sakai 16096–99). In addition, an ever-growing body of research indicates that disruptions in the pruning process (in children and adolescents) may expose the brain to potential manifestations of neurological disorders (Sakai 16096–99).

Healthy cell proliferation and apoptosis are observed in normal hippocampus development; this frames the hippocampus as an extremely sensitive region to cancer therapies targeting rapid cell growth. Chemotherapy and radiation therapy are potent at targeting cancer cells but often do not spare healthy proliferating cells. According to Jones and Pattwell, chemotherapy-induced detriments in rodent models reveal anti-proliferative effects in the hippocampus that linger for up to 6-months after chemotherapy treatment.
Myelination, synaptic pruning, and cell growth and death are three normal processes involved in hippocampal development.

From a physiological perspective, smaller hippocampal volumes are seen in PTSD-affected adults than healthy controls (Marusak et al.). It is hypothesized that such volumetric alterations in the hippocampus are linked to dendritic atrophy, neurotoxicity, and decreased neurogenesis (Marusak et al.).

In a review by Dietrich et al., the effects of chemotherapy on the hippocampus are examined on a holistic level. By considering a large body of research and preclinical studies, Dietrich et al., concluded that cognitive dysfunction after chemotherapy is correlated with structural and functional changes in the hippocampus, including impaired neurogenesis.

Other brain regions implicated in posttraumatic stress syndrome/posttraumatic stress disorder:Carrion et al. conducted an fMRI (functional magnetic resonance imaging) study where healthy controls and PTSS/PTSD affected youth engaged in a behavioral inhibition task. The study results revealed hyperactivity of the dACC in PTSS/PTSD affected youth compared to the controls (Carrion et al. 514-26). The dACC's functions include cognition, motor control, and emotional processing (Bush et al. 523-28). Carrion et al. discovered that both the healthy control group and the PTSS/PTSD affected youth had similar performance in the task— there were no disparities in speed or accuracy among the two groups. However, the fMRI scans revealed that the PTSS/PTSD group had to commit a higher level of dACC engagement than the healthy control group. This finding indicates that the hyperactivity of the dACC is a compensatory mechanism employed to make up for neurological detriments because of trauma (Marusak et al.). Marusak et al. expand on Carrion et al.'s findings, stating that this aberrant dACC engagement can be placed in context to the neurotoxic effects of cancer therapies.

Aversive learning, fear extinction, and posttraumatic stress syndrome/posttraumatic stress disorder:Aversive learning refers to the conditioned aversion from an event by pairing it with a negative stimulus (Andreatta, Marta, and Pauli). Fear extinction is the ability to decrease fear response after the event is no longer followed by negative stimuli. Aversive learning and fear extinction provide valuable insights that help us understand the mechanisms of PTSS/PTSD induced by cancer treatment (Jones and Pattwell. 100657). In the context of cancer treatment, pediatric patients can develop an aversion to sights, sounds, or smells that trigger fear memories associated with their cancer treatment. Alterations in the amygdala-prefrontal wiring may impede the functions that underlie fear extinction, which is foundational for PTSS/PTSD manifestation (Jones and Pattwell. 100657). The hippocampus also has an established role in fear extinction, as it is responsible for memory consolidation and, by extension, fear memories. The amygdala-prefrontal connections and the hippocampus create a system that controls successful fear extinction and are thus vulnerable to chemotherapy and other cancer treatments.

Cancer-related distress among adolescents and young adults:

Cancer-related distress encompasses a wide range of psychological outcomes, including PTSS/PTSD. This section covers several other areas of cancer-related distress often reported by pediatric cancer survivors.

In an analysis by Shay et al., a 2010 LIVESTRONG survey for Post-Treatment Cancer Survivors revealed that adolescents and young adults reported the highest levels of FOR (Fear of Recurrence). 85% of adolescents and young adults reported FOR, and 79% of older survivors reported FOR (Shay et al. 4689-96). The results of this study emphasize the criticality of survivorship care that satisfies all psychological needs of this population (Shay et al. 4689-96). Depression in adolescents and young adults who survived cancer is also observed. In a study, Huang et al. assessed the quality of life for adults who experienced childhood cancer. Of 1,667 participants (over ten years since survival), 15.8% met the criteria for clinical depression (Huang et al. 4242–51).

Study One: Pediatric brain tumors treated with cranial irradiation. Radiation therapy involves using high doses of radiation to eliminate cancer cells. The younger the patient (less than five years old), the higher the probability of brain damage.

A 2018 cross-sectional study by Neu et al. investigates the late effects of cranial irradiation in pediatric brain tumors. The study utilized susceptibility-weighted MRI (magnetic resonance imaging) to examine cerebrovascular complications, which can contribute to cognitive impairments (Neu et al. 280-86). A cohort of twenty-nine former medulloblastoma (MB) patients (treated with cranial irradiation) was selected to participate in the study. An additional eleven patients who had pediatric brain tumors other than MB also participated (treated with radiation, surgery, and chemotherapy). Of the patients assessed, the mean age at diagnosis was 8.7 years, and the mean age of follow-up was 22.2 years.

The MRI results showed that 90% of former patients exhibited Cerebral Microbleeds (CMB), with a mean number of 36 microbleeds per patient (Neu et al. 280-86). These observed lesions are well-established to be accompanied by other neurological risks. According to Neu and colleagues, CMB may be the underlying cause of deficits in processing speed, attention, and other cognitive functions. The main takeaway from this study is an association between cranial irradiation for pediatric brain tumors and the prevalence of CMB (Neu et al. 280-86). Ergo, the development of CMB after this treatment should be regarded as an increasing threat to the

quality of cognitive function in pediatric patients, and the knowledge of these risks should guide future radiotherapy practices.

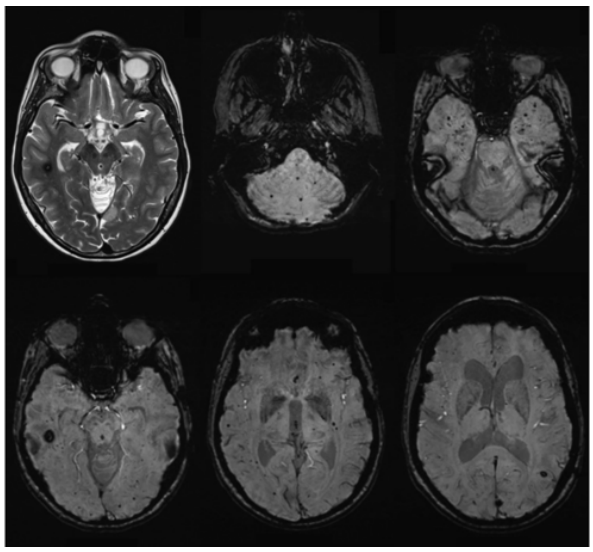

Figure 4. MRI revealed cerebral microbleeds in a 37-year-old, 28 years after surviving childhood cancer.

Figure from "Neu, Marie A., et al. "Susceptibility-Weighted Magnetic Resonance Imaging of Cerebrovascular Sequelae after Radiotherapy for Pediatric Brain Tumors." Radiotherapy and Oncology, vol. 127, no. 2, 2018, pp. 280–286., https://doi.org/10.1016/j.radonc.2018.03.010."

Study Two: Childhood Acute Lymphoblastic Lymphoma treated with chemotherapy only
In this study, Liu et al. found that exposure to higher concentrations of chemotherapy agents like methotrexate put the pediatric patient at higher risk of developing neurocognitive deficits.
The objective of this study was to examine the evolution of neurocognitive functions on a large sample (158 participants) of childhood Acute Lymphoblastic Lymphoma (ALL) cancer survivors treated with chemotherapy. The results showed that survivors who had poor sustained attention at the end of their treatment improved with long-term follow-up (Liu et al. 398-406). Furthermore, the long-term follow-ups indicated that most survivors recovered significantly from attention deficits at the end of treatments; however, there was a higher frequency of executive function

impairments than the general population. In addition, patients exposed to higher levels of methotrexate, a chemotherapy agent, and given intrathecal chemotherapy treatments ("intrathecal," meaning, via spinal canal injections) exhibited "executive dysfunction and slower processing speeds" (Liu et al. 398-406). In this context, executive function means the development of self-regulation, inhibitory control in early childhood (Liu et al. 398-406).

Study Three: Surgical resection and other factors as a predictor for posttraumatic stress syndrome

This longitudinal study aims to assess several outcomes in cancer survivorship among adolescents and young adults.

First, Kwak et al. examine the prevalence of PTSS 6 and 12 months after diagnosis and the risk of PTSD (PTSD is more severe than PTSS and is characterized by longer illness duration) at 12 months. Second, they observe the changes in PTSS throughout the first year of diagnosis. Third, they assess the health variables involved in the manifestation of PTSS. According to Kwak et al., patients diagnosed with cancer in their adolescent or teenage years are more likely to experience distress due to disruptions in their social and psychological maturation. In the study, 151 survivors participated and provided Kwak et al. with self-reported data.

At 6 months post-diagnosis, 39% of patients reported moderate to severe PTSS. But at 12 months, that figure increased to 44% (Kwak et al. 1798-1806). According to regression analyses, factors like having surgical treatment or currently receiving treatment were associated with higher levels of PTSS (Kwak et al. 1798-1806). Nevertheless, while surgical resection (the removal of tumors, tissue, or organs) is included in the list of predictors, it is part of a more extensive list that includes other non-treatment-related factors. This should be considered, as it underscores that factors outside of treatment may also correlate with PTSS/PTSD incidence in cancer survivors. It is also necessary to consider another caveat in this study that limits forming conclusions that apply to the whole pediatric cancer survivor population: while encompassing some pediatric ages, the age group represented by this study (14 - 39 years) extends beyond the pediatric window for this review.

Future considerations for the psychological and physiological well-being of pediatric cancer patients:Jones and Pattwell discuss that most studies combine children and adolescents into one study, which makes it difficult to disentangle the varying developmental trajectories. Thus, it is imperative to design studies that account for the developing nature of the brain across different age groups (Jones and Pattwell 100657). In turn, this enables us to frame psychological

intervention in the context of the pediatric brain's developmental period and provide tailored intervention.

In their review, Marusak et al. also call for similar steps to be taken. Future studies should focus on distinguishing between the neural well-being of three groups: healthy controls, cancer survivors with PTSS/PTSD, and cancer survivors without PTSS/PTSD. Furthermore, in cancer survivors without PTSS/PTSD—researchers should examine compensatory mechanisms in the brain that provide security from psychopathology (Marusak et al.). Finally, external factors to treatment such as sociodemographic status, family/friends networks, etc., should be considered for future studies and practices.

Conclusions

The Centers for Disease and Control (CDC) report that cancer mortality in adolescents is decreasing while cancer incidence is increasing (CDC.gov). This means that more children and adolescents are being diagnosed with cancer, and more are surviving. These promising survival rates also mean more children and adolescents are at risk for neurological impediments post-treatment. This review focuses on two brain regions afflicted in the development of psychopathology: amygdala-prefrontal connections and hippocampal connections. Three cases outlining the outcomes of cranial irradiation, chemotherapy, and surgery demonstrate the risk for each of these commonly used therapies in the development of neuropathology post-treatment. As noted, these studies, while highly insightful, also have limitations. Thus, it is imperative to tailor studies to specific age groups, developmental time points, and other factors.

Modern medicine has a growing inventory of therapies and treatments that effectively eliminate cancer. Compared to a mere fifty years ago, we have achieved significant milestones, and we can continue to advance the field of pediatric oncology by directing our focus to mitigate and minimize risk for neuropathology post-treatment.

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Investment Risk & Reporting Variance: The Necessities of ESG Regulatory Reform by Junhee Hwang

Introduction

Recently, investors' burgeoning interest in ESG funds, equity portfolios or bonds that integrate environmental, social, and governance factors into the investment process, is well reflected in the sector's exponential growth. Indeed, assets under management (AUM) managed under sustainable investing strategies in the United States has reached $17.1 trillion as of the end of 2020 (Forum for Sustainable and Responsible Investing), and ESG-linked investment products attracted $134 billion in net inflows in the third quarter (Morningstar, 2021). Another way to phrase this: one out of every three dollars under professional management in America (Vox 2021) is now, at least in part, invested in assets vetted for ESG qualifications.

However, it has been validated through numerous academic studies that both professional and retail investors prefer a more informative regime, whereas corporate executives strictly prefer fewer disclosures *ceteris paribus* (Hermalin & Weisbach, 2012). Such a collective choice problem leaves both professional and retail investors in a vulnerable situation where they cannot make an accurate market-based response to firms' ESG performance, undermining investment efficiency, which, naturally, the U.S. government seeks to prevent. Viewed from this perspective, regulatory reform impacting the ESG reporting framework in the U.S. markets seems inevitable.

In fact, numerous regulatory bodies have already begun implementing regulations or additional guidelines affecting ESG reporting that could promote further ESG disclosures, prevent greenwashing, and enhance investment efficiency. The U.S. Securities and Exchange Commission created a Climate and ESG Task Force in its Division of Enforcement in March 2021, and the US Treasury Department has called for enhanced disclosures (U.S. Department of Treasury, 2021). Further, in response to firms' indifference towards ESG concerns caused by the government's lack of explicit guidelines, the White House announced executive orders implementing a "whole of government approach" to climate change in January 2021, while the Department of Justice's Deputy Attorney General announced that the agency is taking aggressive new actions for environmental justice (Barcwell, 2021). Even Nasdaq, a private exchange, has implemented board diversity rules requiring listed companies to have at least one "diverse" board member by 2023, and two by 2025 (Nasdaq, 2021).

International ESG regulatory reporting measures have historically been more stringent than those in the States. The International Financial Reporting Standards (IFRS) Foundation, an NGO organization that sought to "develop a single set of high-quality, understandable, enforceable and globally accepted accounting and sustainability disclosure standards—IFRS Standards—and to promote and facilitate the adoption of the standards" (IFRS, 2021), established a sustainability standards board. Similarly, the EU (European Union) adopted a proposal for a Corporate Sustainability Reporting Directive (CSRD), which would amend the existing reporting requirements of the Non-Financial Reporting Directive (NFRD), requiring all large companies to report according to mandatory EU sustainability reporting standards. Despite differences in severity, all of these new regulations aim to establish more quantifiable data through a consistent ESG disclosure framework and a clearer definition of ESG.

Without explicit definitions and guidelines regarding ESG reporting established through regulatory reforms, firms are incorporating the name 'ESG' in their funds, giving false reassurance to investors that an investment product incorporates ESG criteria. Current ESG regulation enables corporations and investment firms to rely on various frameworks, definitions, and ESG rating providers when preparing reports. This alters the purpose of ESG reporting from being a risk-mitigating supplement to Generally Accepted Accounting Practices (GAAP) – a similar body to the aforementioned IFRS, which works to standardize financial reporting – to being a trap for investors in that it encourages misevaluation of a firm's ESG performance, leading to adverse investment decisions. Nell Minow, core founder and direction of GMI rating from 2010 to 2014 and currently a vice-chair of ValueEdge Advisors, criticizes the lack of a clear definition of ESG by comparing the status quo to "the 1970s when the government was like, 'hey, there's a definition to that word [organic].'" For instance, iShare ESG Aware MSCI USA ETF experienced a dramatic inflow from marketing despite its investment in fossil fuel, gambling, and military industries (MarketWatch, 2021). Such labels have been condemned by authorities both in Europe and the U.S. for their potential to mislead investors, with critics arguing they force investors to pay unreasonably higher management prices and make adverse investment decisions. According to Bloomberg articles such as *Many ESG Funds Are Just Expensive S&P 500* and *Cleaning Up ETF ESG Greenwashing*, some "ESG funds charge outrageous fees for tiny adjustments to the S&P 500" and include greenwashed companies —

companies made to seem more sustainable than reality for marketing purposes — in their mutual funds.

One cannot give a definite answer to whether such funds' high cost is due to legitimate reasons such as developing screen companies – companies that exclude or include stocks based on stocks' exposure to certain characteristics or factors (MSCI, 2021) – or simply a malicious attempt to exploit investors' goodwill to invest ethically; however, it is clear that an increasing number of companies, including well-known large-cap corporates such as ExxonMobil and Microsoft, are engaging in potential 'greenwashing' practices. For instance, ExxonMobil received a BBB rating, where ratings CCC and B are considered 'laggard,' BB, BBB, and A considered 'average,' and AA and AAA considered as 'leaders' of ESG, from MSCI for advertising their involvement in developing sustainable algae fuels (BBC, 2021). This is despite "[the] reality of their business model [which] is to continue to exploit, develop and sell oil and gas" according to Dr. Naomi Oreskes, a professor at Harvard University whose research focuses on the Earth and environmental sciences. Another example of greenwashing prevalent among big tech companies is abusing the ESG composite score process. Recently, Microsoft utilized its natural advantage of making a small environmental footprint compared to other industries to propose ambitious environmental commitments such as becoming "carbon negative by 2030" (Microsoft, 2020) to receive an above-average ESG score of AAA. While at first glance this may seem fair, one must keep in mind several social and governance risks the company purports. Indeed, an AAA rating has been assigned to Microsoft regardless of their user privacy issues and the company's combination of CEO and Chairman roles (WSJ, 2021). On the latter point, Microsoft's fiduciary responsibility to its shareholders is arguably not upheld in this case, when scholars have posited: "shareholder returns over an extended period seem to be favorable for those companies which separate the CEO and chairman roles" (Noked, 2012). Such a trend toward masking a company's true ESG performance is not to be taken lightly as numerous empirical studies and research papers collectively demonstrate that ESG factors are, in fact, materially correlated to both equities and fixed income performance (UN Global Compact, 2018).

So, will an ESG regulatory reform that standardizes the ESG disclosure framework, eliminates composite ESG scoring, and defines what applies as ESG effectively push companies

to follow ESG guidelines and hamper greenwashing? Additionally, will this reform that eliminates investors' risk of misevaluating a firm's performance ultimately benefit investors?

Investors are pouring trillions of U.S dollars into sustainable investing funds, and financial experts are raising concerns about the recent trend. As those without the capacity to provide a market-based response argue, it is the government's responsibility to make sure investors could maximize profits without externalizing costs onto the public (Minow, 2021). Thus, regulators of the U.S. government should strive to address the issue of standardizing principle-based ESG ratings. A recent study, *Flow-Driven ESG Returns* by Philippe van der Beck, a Ph.D. student at the Swiss Finance Institute, emphasizes the financial consequences of the lack of regulation on ESG reporting: asset managers and investors are prone to misevaluate a firm's performance, leading to unwanted financial decisions. Lack of ESG reporting regulations' blinding effect on investors is well portrayed in *Figure I [Recent Adverse Investment Decision]* where a wide gap exists between the investment returns of a hypothetical ESG-linked product with and without the effects of $20 billion of quarterly inflows. Such massive ESG inflows, a key theme emphasized in this paper, artificially inflate returns on a relative basis and, in turn, hide the overall lagging performance of ESG-taste portfolios. At the same time, if investors were provided with more standardized ESG reporting over the last few years, they would have been able to perceive that the recent outperformance of ESG funds is due to unanticipated environmental concerns (Lee, 2021), not the actual performance of the firms, and make an adequate market-based decision.

Such investment inefficiency is caused in part due to ESG indices' inability to capture a firm's ESG performance correctly. With a standardized ESG disclosure framework, ESG rating providers such as MSCI and Sustainalytics would not have to sort through unstructured and inconsistent ESG frameworks such as the Carbon Disclosure Project (CDP), Climate Disclosures Standards Board (CDSB), Global Reporting Initiative (GRI), International Integrated Reporting Council (IIRC)), and Sustainability Accounting Standards Board (SASB). Different companies choose to follow different frameworks; if this were not the case, then ESG rating providers could extract more reliable data via machine learning, calibrate to industry-specific factors, and confirm scores via analysts and artificial intelligence. These arguably more accurate ratings, benefitting from an increasingly analytical and data-driven approach, can resolve today's investment inefficiency caused by the implementation of different ESG reports. The more

accurate ratings acquired from information provided directly to investors via standardized reporting, instead of from various speculations, can then be utilized for indices such as Bloomberg MSCI Socially Responsible Index, Bloomberg MSCI Sustainability Index, and Global Sustainability Signatories Index, ultimately increasing investment efficiency. Currently, although artificial intelligence employed by various ESG rating providers in an effort to extract information from various disclosure frameworks provides investors with a comprehensive analysis of a firm's ESG performance, it adds a layer of variability between ESG rating providers. Potentially, such a layer hampers investors from understanding if a firm has solid ESG credentials. With a standardized ESG reporting framework, investors would be able to enjoy not only a comprehensive analysis of a firm's ESG performance but also constant ESG scores from various rating providers.

The effects of the EU's Non-Financial Disclosure Directive 2014 – a 'comply or explain' system that clearly defines what large companies are obliged to disclose: environmental matters, social matters and treatment of the employee, respect for human rights, anti-corruption and bribery, and diversity on company boards in terms of age, gender, educational and professional background – reflects regulators' initial attempts at taking steps to further standardize ESG disclosures, in response to the problems cited earlier in this paper around the lack of such regularity. This underscores the urgency and lays out an initial template for U.S. regulators to implement regulations that standardize the ESG disclosure framework, define ESG requirements, and prevent composite ESG scoring which potentially provides firms, particularly larger corporates, the chance to inflate ratings as was mentioned in the earlier discussion on Microsoft.

As a majority of European companies (59%) used GRI's framework for their disclosures under the Non-Financial Reporting Directive of 2014 (Alliance for Corporate Transparency), the effects of the NFR Directive qualify as a case study to evaluate the pros and cons of a situation where a standard ESG disclosure framework *and* the expectations for ESG disclosures are explicitly provided by the government. According to the World Bank, firms that were the subject of the NFR Directive, or treatment firms (such as Philip Morris and Guess), steadily improved their ESG disclosure quality over time compared to firms that were not (such as Chevron and Costco). These points are reflected in *Figure II. [Effect of Regulation in ESG Disclosure]* and make clear the efficacy of multi-national governing institutions like the NFR Directive. A comparison of corporate investment behavior prior to and after the implementation of the NFR

directive yielded favorable results to investors. Underinvested firms, such as the sample firm in *Figure III. [Rise in Investment with ESG Regulation]* that experienced a 45% increase in investment level over merely 2 years – "increased their investment levels by 6.3% of total assets after 2014 relative to the control firms." Further, ESG disclosure scoring did not lead to the issuance of equity, which could dilute the value of investors' existing shares (Investopedia, 2021). The benefits brought by the NFR directive were not restricted to solely equity investors as underinvested firms were able to raise 8.7% of debt relative to the total asset through increased transparency, thereby improving liquidity, lowering capital cost, and improving firm value. Granted, some companies that already disclosed their ESG information experienced negative externalities in the race for better ESG reports than their competitors. That said, the initial cost of adhering to this rule will undoubtedly be offset in the near future through better environmental, social, and governance practice and overall improvements in firm values across the board.

The efficacy and importance of ESG reporting in evaluating risk and return are validated through recent studies. According to a paper published in *Sustainability Accounting, Management and Policy Journal* by Michael Magnan and Hani Tadros, better disclosure of environmental performance via 10-K and sustainability reports correlated with better performance at the 78 companies in environmentally sensitive industries that they examined (Tadros & Magnan, 2019).

Some economists might argue that a standardized ESG reporting framework could undermine U.S companies against others in the global market where their regulations might not be as strict and raise the bar for start-ups as they would have to qualify for more regulations. However, since firms complying with the environmental protection standards will improve their market share, bargaining power, and profitability in the long term (CFA Institute, 2018), forward-thinking ESG policies would benefit everyone by providing higher returns for investors, increasing profitability for firms, and improved tracking of ESG guidelines for the U.S. government. Granted, unification of various ESG reporting frameworks, defining ESG, and eliminating ESG composite scores will require a lot of work; however, as was seen with credit exposure reporting, which helped lenders control credit exposure and control borrower risk, revised ESG reporting policies holds the potential to revolutionize the U.S. financial market. It is up to U.S. lawmakers to recognize the incentives presented throughout the paper to institutional

investors, retail shareholders, and firms themselves and strive to jump over a difficult but rewarding hurdle of mandating material ESG regulation.

Figure 1. *Recent Adverse Investment Decision*

Figure 2. *Effect of Regulation in ESG Disclosure*

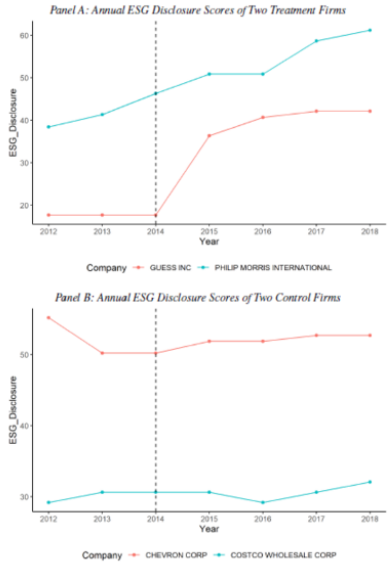

Figure 3. *Rise in Investment with ESG Regulation*

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Positive Psychology: Social Comparison Increases Stress and Self-Deprivation Among Teenagers in Urban Areas by Lichao Wang

Introduction

Positive psychology defines positive mental health and aspects during daily life, which also includes how stress and resilience measure happiness. Moreover, positive psychology describes how happiness influences people differently. Middle- or upper-class teenagers that live in big cities are generally defined as rich, spoiled, and without anxiety because they are protected by their parents and have a wealthy background. However, there are lots of adolescents in cities who are experiencing depression from the stress that they are having.

"Social comparison theory is the idea that individuals determine their own social and personal worth based on how they stack up against others" ("Social Comparison Theory"). Social comparison occurs among teenagers in urban areas from school performances, social media, and family factors. Living in big cities such as Shanghai sometimes can be influential to teenagers' mental health development. Teenagers have fewer time for physical activities and leisure time in urban areas than rural areas (Regis, M. F. et al.). From the stress and comparison in the environment of the society, teenagers in urban areas are more likely to have depressed parents and high pressure from their families than rural areas (Antaramian, S. P., Huebner, E. S., & Valois, R. F. 2008). Life events, social support, and the purpose of life are factors that strongly affect teenagers, which includes living environment, everyday needs, and school performances (Rask, K., Åstedt-Kurki, P., Paavilainen, E., & Laippala, P. 2003). Besides, social comparison between teenagers causes stress as much as adults face, although it has not been taken enough care. Family, peers, and academic environments in big cities encourage social comparison, which increases stress and causes increased negative feelings and decreased self-esteem.

Increased Stress

In urban areas, family and school performances add stress among teenagers and create conditions for social comparison. Families put stress on young adults intentionally and unintentionally. Parents have experienced difficulties and worry that the same situation will occur in their children again. Consequently, they put high expectations on their children, wishing that they can achieve, however, without realizing how much pressure they put on them (Hesketh,

T., & Ding, Q. J. 2005). Some parents make their children learn skills that they have no interest in, such as instruments and academic subjects. With their life under the pressure of high expectations, some teenagers feel over-controlled by their parents. However, there are factors related to resilience due to high expectations from families. Some families that have multiple children do not put all the pressure on one child, so children do not feel as much stress as some single-child families. Some parents also do not put the stress on their children to provide the freedom of choice. Therefore, their children can learn hobbies and enjoy activities that they like (Hesketh, T., & Ding, Q. J. 2005). Furthermore, parents are models of children. Although parents are not always perfect, their kids still copy what they have done. For example, when parents visit their family during holidays, they compare their children to children of other families. Consequently, teenagers follow what their parents do and compare themselves to their peers. With the knowledge of comparison, some children compare themselves with their friends at school. Frequently, they feel stressed out by the fact that other students sometimes have better performances than themselves (Miao, H., Li, Z., Yang, Y., & Guo, C. 2018).

In addition, in urban areas, children are more likely to have depressed parents, due to the high pressure of competition in cities. Parents' mood and attitude affect teenagers' feelings directly. Occasionally, when teenagers observe the negativity from their parents, anxiety increases among themselves. (Hesketh, T., & Ding, Q. J. 2005).

Moreover, school performance encourages comparison and stress. Most adolescents in urban areas are well-educated and have high goals to achieve; for example, well-known colleges or studying abroad. The competition and comparison can be encouragement but also anxiety. As students, adolescents compare their school performances by their grades and teachers' reflections. They have to work hard at school and home to achieve both. Schools in urban areas generally increase the hardness of work year by year, for better outcome and knowledge for the students. However, the complicated schoolwork provides increased stress and anxiety (Hesketh, T., & Ding, Q. J. 2005). They have to work harder and sometimes take extra classes outside of school to accomplish a higher grade. In some schools, teachers have biases on students that do not have outstanding performance. Adolescents are sensitive; therefore, social comparison can be harmful and unsatisfying.

Decreased Self-esteem

In cities, social comparison increases teenager's sense of personal deprivation and decreases self-esteem. Students question themselves at school and increase their pressure from other students. When they have a lower grade, they feel depressed among their peers. "Comparison of ability means that an individual tends to compare his/her abilities and achievements with those of others, while comparison of opinion means that an individual tends to compare his/her ideas and beliefs with those of others" (Miao et al. 2018).In schools, both comparison of ability and comparison of opinion occurs frequently. When a student has better ability, he or she usually has strong leadership and guides other students. The advice helps students that do not work as well but also increase their sense of personal deprivation. Furthermore, comparison of opinion between teenagers can be disadvantageous when teachers have bias on students. As an instance, during discussion of ideas, teachers can call on an outstanding student rather than an unremarkable student, which decreases some teenagers' confidence. Some teenagers have excellent grades but when they see their peers that are not as well, sometimes they change themselves to fit in the atmosphere. The process of changing themselves is called self-adaptation, in this case, it describes the situation when a student loses his or her confidence to fit in the environment.

In addition, social media increases comparison by the posts that other teenagers post. In cities, adolescents meet people from different ages, cities, and families. Some teenagers compare their family economic background, clothing, and appearances. Social media has become a perfect place for comparison because it is easy to view everyone's daily life and lots of people use it. Some teenagers feel depressed after surfing on social media because they feel unrelated and excluded from their friends (Steinmayr, R., Wirthwein, L., Modler, L., & Barry, M. M. 2019). Using social media provides benefits for the ease of communication but also drawbacks when social comparison occurs.

Discussion

"Adolescence is today defined as a distinct period of adjustment or as a journey to adulthood where a teenager has to face rapid physical, cognitive and social changes" (Rask et al. 2003). When adolescents face changes, schools and parents should take care of their mental development. Schools should teach teenagers about empathy in order to decrease comparison

and increase caring among them. Empathy is important for teenagers because during adolescence, they are sensitive to statements and opinions. Learning empathy allows teenagers to treat others better and increase happiness by understanding and caring (Authors Mojtaba Soltanlou, Authors Abbie Jordan, Authors Jonathan Levy, & Authors Kathryn Mary Broadhouse). As an example, when a student feels bad from comparison to other exceeding students, by learning empathy, the exceeding students might advise and guide him or her. Schools should also teach students to gain self-esteem, to know their worth in society and school. Increasing self-esteem can also decrease the stress from social comparison. At schools, teachers should treat students the same, to increase their confidence. In order to avoid increasing social comparison, teenagers should care more about themselves instead of comparing themselves to others. Society is more accepting and understanding due to their sensitivity and adoption of information. The age of adolescence is mainly learning and adopting information to prepare for their adulthood. Learning how to treat others as well as themselves is important (Steinmayr, R. et al. 2019). Bringing positivity and teaching empathy can show the adolescents how they should treat others and react to life events.

Conclusion

"High social comparison frequencies may be correlated to undesirable results, such as feelings of academic inferiority, low happiness, poor self-perception, low self-esteem, and social anxiety" (Miao et al. 2018). Social comparison brings out negative effects on adolescents which increase their stress and decrease their self-esteem. As an important stage of life, society should take care of adolescents and teach them how to increase self-esteem during daily life. Sometimes, families put too much pressure on teenagers and should give teenagers options to decide by themselves. There are ways to achieve goals and ideal grades, teenagers should increase their self-worth by working harder and understanding others. When adolescents question their ability, they increase their sense of self-deprivation which can be harmful for their mental health. Studies have shown the negative side of social comparison; however, it can also increase competition and promote efforts in the future.

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Benefits of Music During The Pandemic: How Music Connects the Souls of the Population Into One Feeling During Rough Times by Om Guha

Introduction

COVID-19. For the past 16 months, this pandemic has caused mass instability around the world socially, economically, and politically. To add on, the mental toll that the pandemic has caused on humankind, specifically the frontline workers, infected patients, and patients that have recovered, but yet still have recurrences of their abhorrent time with the pandemic. Because of how taxing the duties of frontline workers are, and how the positive patients who are in serious condition suffer, the mental stability of these people decrease, and this can affect their productivity in their jobs, their attitude around their loved ones, and the way they approach their ideals. These people are also conflicted with distress, and this is a direct effect of COVID-19. However, there are many art forms that therapists can implement into their practice, and music is one of them. Ever since ancient times, music has been an integral part of the existence of humankind, and it has been evolving for eons to please the ears of the people who listen to it. But the real question is: How does music contribute to relieving the stress of humankind during a difficult pandemic like COVID-19?

How Music is Keeping Us Connected During the Lockdown

While the pandemic has caused widespread lockdowns all around the world, that does not mean that the connection we have with each other has been severed completely. According to Jessica Pouranfar from Northwestern University's music department, music has maintained the connection between the international population even during worldwide lockdowns. She also posted that the number of social media posts related to music increased by over 60%, with a vast preponderance of the international population posting videos related to music in some way or form. Pouranfar also states that the more people post music videos on social media, the more connected the world will be, even during nationwide lockdowns that incapacitate the peoples' ability to get together for events. People on social media can respond to each other, comment on posts, and even propose musical collaborations. The entire world can connect through one common language: Music. Especially during a time like now, people require some sort of connection to keep themselves acquainted with the others around them.

The Stress-Relieving Properties of music

As time has passed, music has been hailed as a force that can heal through the soothing of the nerves. Many desperate nations are still hung up on expensive treatments and stress-relieving programs. According to the World Economic Forum, In 2020, stress management expenditures for the US alone hit an all-time high of $190 billion dollars, and 10% of that amount was spent on healthcare. As far as the pandemic is concerned, out of the $2.59 trillion that the US Government has spent in the span of 16 months, about 7%, or $180 billion of that expenditure was for stress management. The World Economic Forum implies that the healthcare for stress expenditure can be reduced by almost 70% just by using music therapy as the primary. Music therapy has been increasing in credibility after various case studies conducted around the world have proved to be successful in relieving the stress of patients afflicted with chronic diseases, and now this same trend is being seen in patients afflicted with COVID-19. Music therapy was started by Everett Thayer Gaston, a psychologist who wanted to see if music could affect human behavior. He had successfully determined how the human brain reacts to music, and how it can be used as a medicine. Now, many therapists have built on his research, exploring the vast variety of uses that music has, especially in the medical field. Music therapy, if at its full potential, can help soothe the tense nerves of the frontline workers, who work day and night to save the lives of the infected, regardless of their financial and social status. To add on, music can induce the release of stress-relieving hormones such as dopamine, oxytocin, and serotonin, which help alleviate stress and anxiety, which is a direct result of the nervous system activity getting lower. When the activity of the nervous system is lower, then people, regardless of whether they are patients or regulars, have less anxiety and are thinking less about a multitude of stress-inducing factors that can hamper them from carrying on with their lives.

Conclusion

It has been proven that music is an art form that can be used for multiple purposes. Music has proven to be a strong stress reliever that can be implemented in various environments. It is flexible to all of our needs, and through further research, we will be able to save more money on expensive cures to diseases and stress-relieving programs by deeming music as a definite cure to a myriad of diseases. As a community, all of us can write our history with music, and showcase

its power to the whole world. Till now, the art of music was a hidden language, but now, it will become a common language that can link all of us and greatly lower the stress of people who are constantly fighting battles with themselves. Dr. Tom Sweitzer has delved even more into the actual link between music relieving stress. He has identified that Music can actually improve our brain linkage by linking our neurons, and that can keep our mental composure together. When neurons are linked, our thinking is more rational as we are relaxed and completely open to making the correct decisions in life.

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British Colonialism in India: A Triumph or Tragedy by Om Guha

Introduction

India, a nation that flourished with wealth and riches, was the epitome of civilization and culture. First, they were divided into many kingdoms, then united under one flag under the Mughal Empire, which used their treasury to modernize and cultivate the economy and culture of the nation. However, as Mughal Emperor Aurangzeb took over the reins of the empire from his father Shah Jahan, the entire country was thrown into turmoil. He caused the mass killings of 3 million Hindus and other religious minorities throughout his entire reign from 1658-1707. Then, the British Empire, in the form of its subsidiary the British East India Company, started in 1680. Initially, it was meant for commerce purposes only, but with the decline of the Mughal Empire after Aurangzeb's death, the British Empire started to take over Indian land via its subsidiary, the British East India Company. The British colonialism in India was precisely a British Triumph and an Indian tragedy as the British completely looted and pillaged India of her riches, enacted intolerable laws that prompted political instability, and destroyed Indian native culture.

The Indian Economy's "Dark Age".

The British Empire had completely plundered India of its riches and reduced it to one of the poorest nations in the world after independence. In 2017, Dr. Shashi Tharoor, former UN Under-Secretary General, and Indian Congressman, in his speech at Oxford University stated that "India had accounted for over 30% of the Global GDP in 1700, but that figure was reduced to just a mere 3% in 1947. This was caused by the constant looting of the British, and the British do owe reparations for this." This clearly shows how much India was drained of its resources by the British, and how the superiority complex contributed to the looting of India. According to The Times of India, "The British had looted a total of $45 trillion in today's money from India in 150 years of rule." To add on, the once-thriving industries of India laid in ruins after the British destroyed them and established their industries. According to the Asian Century Institute of London, It was mentioned that "The British took thriving industries -- like textiles, shipbuilding, and steel -- and destroyed them through violence, taxes, import tariffs, and imposing their exports and products on the back of the Indian consumer. They taxed the Indian peasantry at a level unknown under any other rulers, and through torture and cruelty they extracted vast sums

of money which they shipped off to England." The British had also imposed import tariffs on the thriving Indian industries, which drove them into loss because of the higher price of goods, and they put their exports on the market and forced Indians to buy them, thus replacing the Indian "swadeshi" industries with their "vilayati" goods and boosted their profits in India, which would all be sent to London.

Political Injustice in British India

India was devastated by the intolerable laws imposed by the British Empire. As Mahatma Gandhi had incited the Indian freedom movement through passive resistance and peaceful protests, the British had taken drastic measures to stop him. They passed the Rowlatt Act on the 8th of February 1919, right after the first world war. This act gave the British immediate powers to jail protesters for up to two years without a trial and banned any social gatherings. To add on, the British caused a massacre on the 13th of April, 1919 at Jallianwala Bagh in Amritsar, Punjab. Dr. Shashi Tharoor states that "The atrocious actions of the British at Jallianwala Bagh displayed how inhuman and cruel the British truly were." This displays how this unlawful massacre of 400 men, women, and children was a strong indication of how India was ruined politically. In the year 1943, during the Second World War, the British failed to provide provisions of food and healthcare to the regular Indian population as due to the war effort, they had prioritized saving food and giving good healthcare to the military personnel and their own citizens sitting back in Britain. The people of Bengal were completely deprived of these necessities and almost 3 million succumbed to this man-made disaster. According to the Independent, Dr. Shashi Tharoor puts Winston Churchill in the category of the worst genocidal dictators of history, in the same category as men like Hitler, Stalin, and Saddam Hussein. He blames Winston Churchill and the entire British Government for the plight of the people of Bengal. The British enacted several intolerable acts, such as the Simon Commission.

The Death of Indian Culture at the Hands of the British.

Third, The British had completely stripped India of its cultural richness. In 1857, the British had introduced a new rifle, and in an attempt to cause a rift between Hindus and Muslims, the two majority religions of the country said that the rifle had a cartridge that was made from cow and pig fat. In Hinduism, the cow is sacred and in Islam, eating pigs is forbidden. This way,

the Indians in the British Army, also known as Sepoys, were completely divided by religion. The British had done this so that they would be assured that there would be no rebellion. However, they were mistaken. On the night of May 10th, 1857 in Meerut, the Indian sepoys led by Captain Mangal Pandey, openly revolted against their British Masters and shot them dead. Eventually, many brave hearts, such as Rani Lakshmibai of Jhansi took part in this armed revolt. In the end, the revolt had failed, but it gave light to many other freedom fighters, the most famous one being Mahatma Gandhi. Back in 1757, when the East India Company's power in India was on the rise, they had destroyed India's handloom industry, which had been the epitome of Indian culture. India's vibrant handlooms were replaced by cheap British cloth, and in the end, it would just be a source of income for their government, and Indians would not receive any return investment. Dr. Satish Chandra, a well-known Indian Historian has stated, "The once prosperous handloom industry has been laid waste by the British aggressor. The culture of India is like a caged bird, begging to spread its wings to enlighten the people, but confined by the cruelty of British arrogance." The British degraded the cultural value of India, and then used her vast cultures to her disadvantage, as in the partition of 1947. India was partitioned into two nations after independence: India and Pakistan. However, the process was one of the most bloodiest and gruesome man-made ethical conflicts of the 20th century. The partition of India saw mass ethnic cleansing, forced migration, and communal violence between Hindus, Muslims, and Sikhs. Violence was especially prevalent in the Punjab and Bengal provinces, as they had the highest mixed ethnic population, especially in the cities of Amritsar, Lahore, and Calcutta. These three cities were burning with all of the communal violence. Dr. Shashi Tharoor, in a BBC interview, states that the British carelessness of not recognizing the communal disparities between the different religions of India caused India to burn as a direct result of the partition and that the British had "played their trump card" in the destruction of India.

Conclusion

In Conclusion, British Rule in India benefited the British and left a once-thriving Indian population in shambles. This is because the British drained India of its resources caused political disasters by enacting the most intolerable laws that man had never experienced, and divided the country culturally, thus causing the most miserable event: the partition. Although many

historians and proponents of the British Empire argue that the British Empire benefited India, there is no question that the negatives of British Rule outweigh the positives.

Risk of Developing Glaucoma Based on Ethnic Backgrounds by Anusri Koditipalli

Introduction

Glaucoma is the second leading cause of blindness in the world. The disease count is expected to rise over 111 million in the next twenty years. Glaucoma is generally caused by IOP (elevated intraocular pressure). Elevated intraocular pressure is when the pressure in the eye is elevated and above normal eye pressure (Whitney 2020). Normal eye pressure is 10-21 mm Hg. Eye pressure is considered high when it is above 21 mm Hg. There are two forms of glaucoma which are open-angle and angle-closure glaucoma, however each comes with variations (Monica et. al 2020). In open-angle glaucoma, the eye's iris and cornea are open like normal, but the eye's drainage canal becomes clogged over time which causes damage to the optic nerve in the eye. Damage to the optic nerve in open-angle glaucoma will cause eye pressure to increase (William 2019). In angle-closure glaucoma, the eye's iris bulges forward which will block the drainage formed by the cornea and iris of the eye (Roski et. al 2016). Blocking of the drainage will cause the eye pressure to increase. Glaucoma generally affects people of older age, typically above the age of 80, but any age, ethnicity, or gender can be diagnosed with glaucoma. However, the risk of glaucoma from ethnicity to ethnicity does vary, and certain ethnic backgrounds are at higher risk for glaucoma than others. This paper will show what causes glaucoma to be more evident in certain ethnicities. Studies have proven that one ethnicity is at higher risk for glaucoma based on certain features in the eye (Murakami et. al 2011). African Americans are at higher risk for glaucoma than any other ethnicities.

Methods

In order to study the prevalence of glaucoma in racial variations, designs were created to collect the necessary data. The design was a population based survey of a black and white population aged 40 years and older from the eastern and southeastern health districts of Baltimore, Md (Tielsch et. al 1991). To study the racial disparities of glaucoma in regular hospital patients, different designs were conducted. The design was conducted based on 152 individuals with glaucoma. Data was collected via oral questionnaire. Survey results were correlated with follow- up eye examinations (Murakami et. al 2011).

Results

Glaucoma has significantly higher prevalence rates in African Americans. Data sampling showed that 115 of 140 patients (81.6%) with open-angle glaucoma, 221 of 392 patients (56.4%) with ocular hypertension, and 1,028 of 2,109 patients (48.7%) in a random sample were black. In all three cases, glaucoma was almost 50% prevalent in African Americans which clearly shows that racially African Americans are at higher risk for glaucoma. In the same sampling, it was proven that glaucoma's age of diagnosis was earlier in African Americans compared to whites (69.1 years vs. 63.7 years) (Martin et. al 2016). In another study in Baltimore, prevalence rates for open angle glaucoma were four to five times higher in African Americans. Prevalence rates ranged from 1.23% to 11.26% from ages 40 to 80 in African Americans. On the other hand, rates in whites ranged from only 0.29% to 2.16% with the same age groups (Tielsch et. al 1991).

Discussion

Based on this data, it's clear to see the alarming differences. Glaucoma has significantly higher prevalence rates in African Americans even though it is something that develops over time. The population who is told to be at most risk is just generally elder patients. This considered, there are still ethnicities that develop glaucoma at higher rates. This data is important and should not be taken lightly for one main reason; it is clear that there is a higher prevalence rate for glaucoma in the African American race. This prevalent data should be used to expose the importance of African Americans, and all other ethnic groups, to get regular eye checkups to diagnose these diseases before they lead to blindness and other irreversible problems. It is advised that those of all ages, genders and ethnicities should be getting regular checkups to make sure their eyes are fully healthy and functional. My research on this topic as well as my desire to conduct this research paper was influenced by my great-uncle, Shivram Jyothinagaram. This is my maternal great uncle who I am extremely fond of and very close to. He has recently been diagnosed with angle-closure glaucoma, and he is on the verge of blindness. He is 65 years old and has developed glaucoma in the past year. Due to his age, glaucoma may be more common for him. My great-grandmother also developed glaucoma around 20 years ago, and the glaucoma was more severe in her left eye. My great-uncle may have gotten his glaucoma genetically from my great-grandmother as he is her son. My great-grandmother's eyesight is much better now,

compared to when she was first diagnosed as her symptoms have improved. My great-uncle is just one of the many people who may have been able to prevent their glaucoma from reaching such severe rates if he had been keeping his eyes healthy and visiting his ophthalmologist. Everyone on my maternal side of the family is aware that this disease runs in our family, and we make sure to all get checked by our ophthalmologist regularly. By raising awareness of this issue, I hope not only to increase research but educate others who may be at risk.

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Sarcoidosis Rare Organ Manifestation: Musculoskeletal, Ocular, and Neurological Sarcoidosis and Disease Development by Anoushka Krishnan

Abstract

Sarcoidosis is a rare chronic disease of unknown etiology that commonly presents itself as the growth of fluid sacs in multiple organs. Historically known as a respiratory or cardiac illness, recent studies have highlighted the various other presentations of the disease and their asymptomatic tendencies; illustrating the lack of knowledge about sarcoidosis. The purpose of this literature review is to highlight the rarer manifestations of musculoskeletal, ocular, and neurological sarcoidosis, to raise awareness of the anomalies in the disease's development and resulting symptoms. Past studies and reviews about sarcoidosis and its organ manifestations were gathered using PubMed and Google Scholar. Studies were limited to the year 2004 and later. Trends in the literature have suggested that sarcoidosis is difficult to diagnose because of its unknown etiology and diverse presentation in patients. Further research into asymptomatic sarcoidosis and the procedures for diagnosis for different organ systems would be beneficial to understand the disease and its impact.

Introduction

Sarcoidosis is an inflammatory disease of unknown etiology most often characterized by the development of granulomas in various areas of the body. Sarcoidosis is traditionally classified as an inflammatory disease, but has recently been considered as an autoimmune disease. The presentation, severity, and disease course of sarcoidosis vary from person to person. Though the lungs are affected in 90% of sarcoidosis patients, the disease is rarely limited to just one system, and usually manifests differently in each patient (Baughman, 2011). Sarcoidosis is not a terminal disease for most patients, but it is a chronic condition; 10-30% of patients experience a chronic or progressive disease course (Soto-Gomez, 2016). However, depending on the nature of a patient's sarcoidosis, there are cases where it spontaneously resolves itself.
The estimated prevalence of sarcoidosis is between 10 and 20 per 100,000 population, but varies greatly based on organ manifestation, geographical location, and patient demographic (Fritz, 2016). A potential reason for this variation in prevalence is the common occurrence of undiagnosed sarcoidosis cases. However, the disease peaks in adults between 20-50 years of age,

and affects African Americans and Scandinavians more often than other ethnic groups (Soto-Gomez, 2016). Common manifestations of sarcoidosis also vary based on the location, signifying that environmental factors also contribute to the patients of different areas (Prasse, 2016). Sarcoidosis affects more women than men, likely due to hormonal differences and the female predisposition for autoimmune diseases.

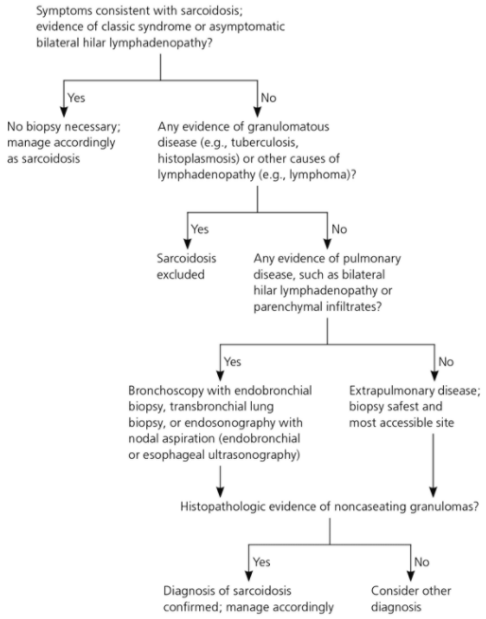

Figure 1: Algorithm for the diagnosis of sarcoidosis (Soto-Gomez, 2016).

Biopsies and scans are usually used to diagnose sarcoidosis, but most diagnoses result from visible symptoms such as bumps on the skin or irritation in the body. Although the cause of sarcoidosis is unknown, the diagnosis methods have highlighted a potential genetic predisposition. The genetic predisposition theory is supported by the different clinical results and disease courses observed in different ethnic groups. Recently, some trends have been observed hinting at the heterogeneity of the disease; 4% of sarcoidosis cases are familial, and approximately 4% to 10% of patients have a first-degree relative with sarcoidosis (Prasse, 2016;Soto-Gomez, 2016). A higher awareness about the sarcoidosis trends in families and ethnic groups could help increase diagnosis rate and early detection.

Although sarcoidosis is a rare disease, there has been an increase in sarcoidosis research in the recent past. However, the majority of sarcoidosis-related literature is focused on either the cardiac or pulmonary sarcoidosis; the common forms of sarcoidosis. This does not usually address the variety and differences in sarcoidosis manifestation. Since it is common

to experience more than one type of sarcoidosis, and there are patients who are affected by rare forms of sarcoidosis, this research is not enough. Rarer manifestations like those in the endocrine system, gastrointestinal system, the kidney, liver, are not well studied and continue to be neglected in scientific literature. The lack of literature is potentially a huge hindrance for diagnosis and proper treatment of rare sarcoidosis cases. Therefore, the purpose of this paper is to increase awareness by focusing on three of the rarer sarcoidosis types: musculoskeletal, ocular, and neurological manifestations.

Methods

A literature review was conducted to consolidate up to date information on sarcoidosis. Past studies and reviews about sarcoidosis and its organ manifestations were gathered using PubMed and Google Scholar. Studies were limited to the year 2004 and later.

Results

Musculoskeletal sarcoidosis describes a manifestation of sarcoidosis in the joints, bones, or muscles. Though less common than pulmonary sarcoidosis, musculoskeletal manifestations still occur in one quarter to one-third of sarcoidosis patients. The disease generally peaks twice, once in young adulthood (20-40) and again at around 50 years (Soto-Gomez, 2016). Unlike cutaneous and cardiac involvement, musculoskeletal sarcoidosis is more common in northern European countries, most frequently in the form of Löfgren's syndrome (Mannes, 2020). Löfgren's syndrome is a multisystem manifestation of sarcoidosis involving erythema nodosum, bilateral hilar lymphadenopathy, and acute arthritis, most often bilaterally affecting the ankles.

Musculoskeletal sarcoidosis varies in presentation for each patient, but can also manifest in polyarthritis and other arthropathies, myopathy, and dactylitis (Mannes, 2020). Further bone and skeletal muscle involvement occurs in many patients, but is often asymptomatic and only diagnosed after imaging. As a result of various manifestations, there is not a clear diagnosis system for musculoskeletal sarcoidosis.

Musculoskeletal sarcoidosis is usually diagnosed after or with pulmonary or systemic sarcoidosis, often as a byproduct of imaging meant for a different purpose. However, some rheumatic involvement does occur independent of or prior to pulmonary involvement and is

diagnosed later as a result. Löfgren's syndrome is often diagnosed through chest x-rays or the obvious and sudden swelling of the ankle due to acute arthritis (Bechman, 2018).

Many instances of sarcoidosis, including 90% of cases of acute polyarthritis, are resolved by spontaneous remission and require no further treatment (Kobak, 2015). No drugs or treatments are specifically approved for rheumatic sarcoidosis, making treatments often case-specific. NSAIDs (non-steroidal anti-inflammatory drugs,) corticosteroids, and hydroxychloroquine are some common drugs prescribed for patients with these manifestations.

Ocular Sarcoidosis

Ocular sarcoidosis describes the manifestation of sarcoidosis in the eyes. There is a large range in data regarding the prevalence of ocular sarcoidosis—ocular prevalence in systemic sarcoidosis patients has been reported to be anywhere between 13% and 79% (Dammacco, 2020). Females with systemic sarcoidosis are more likely to develop ocular manifestations than men. The most common symptoms of ocular sarcoidosis are uveitis, inflammation of the inner layer of the eye, and conjunctival nodules, granulomas that appear on the thin membrane covering the surface of the eye (Pasadhika, 2015). These conditions usually result in redness of the eye, swelling, pain, and altered or blurred vision.

Ocular sarcoidosis is thought to be the presenting sign in 11-30% of sarcoidosis patients who are later diagnosed with extra-ocular disease (Dammacco, 2020). Because of the external symptoms (swelling, redness, loss of vision, pain) of ocular sarcoidosis, it is easier to diagnose than most other organ manifestations.

Due to the complexity and heterogeneous presentation of ocular sarcoidosis, ophthalmologists have had challenges treating the disease in the past (Matsou, 2018). Topical treatment in the form of corticosteroid and cycloplegic eye drops, ocular corticosteroid injections, and ocular implants are common treatment options to relieve pain and treat inflammation (Pasadhika, 2015). Systemic corticosteroids and immunosuppressants are also used to treat patients who are resistant to or whose conditions are too severe for topical treatment (Pasadhika, 2015).

Ocular sarcoidosis can also have connections to other organ manifestations, such as dermatological: ocular surface disease on the eyelid, or neurological: regarding the optic nerve and other neuro-ophthalmological symptoms (Pasadhika, 2015).

Neurological Sarcoidosis

Neurological sarcoidosis, more commonly known as neurosarcoidosis, is used to describe manifestations of sarcoidosis in the nervous system. It affects between 5% and 15% of sarcoidosis patients and is one of the more serious manifestations (Hoitsma, 2004). Due to the discrepancies in neurosarcoidosis diagnosis and the rarity of studies and data, not much information exists concerning its prevalence in specific demographics.

The most common presentation of neurosarcoidosis is cranial neuropathy. This damage to the nerves usually limits motor skills and causes pain, headaches, and weakness. Optic neuropathy is the second most common and usually results in painful loss of vision over time (Pawate, 2009; Hoitsma, 2004). Seizures are a more devastating product of neurosarcoidosis and are associated with higher morbidity rates and longer disease durations (Mannes, 2020).

Neurosarcoidosis is very difficult to diagnose, due to the long-term risks of nerve biopsies and the lack of biopsy evidence for some presentations of neurosarcoidosis (Mannes, 2020). Diagnosis usually relies on the presence of systemic or existing sarcoidosis in patients, but 17% of neurosarcoidosis are thought to be isolated, with no other sarcoidosis involvement (Pawate, 2009). As a product of the challenges of neurosarcoidosis diagnosis, studies have suggested that only 50% of neurosarcoidosis patients receive an antemortem diagnosis (Hoitsma, 2004).

Because of the lack of data about neurosarcoidosis, treatment is usually specific to the patient and experience, rather than common evidence (Hoitsma, 2004). Early treatment is recommended, given the serious nature of most neurosarcoidosis cases. Corticosteroids are the most common drugs used for neurosarcoidosis therapy, and in higher doses, than recommended for other manifestations of sarcoidosis (Fritz, 2016; Hoitsma, 2004).

Conclusion

Like many sarcoidosis-related statistics, reported diagnosis rates of sarcoidosis vary often in research—creating large ranges of data such as ocular sarcoidosis affecting anywhere between 13 and 79% of sarcoidosis patients. (Dammacco, 2020). Most people diagnosed are those with visible symptoms, and diagnosis for patients is always different based on the presentation of the disease. A potential reason for these nonspecific, large ranges is the potential of asymptomatic sarcoidosis cases. Though not all asymptomatic cases are serious or life-threatening, a lack of

diagnosis almost certainly means a lack of treatment and misrepresentation of how many people the condition truly affects.

Because of the extremely variable nature of sarcoidosis and its presentation, treatment is almost always case-specific. Within each manifestation are secondary conditions that end up getting treated—such as eye drops for swelling in ocular sarcoidosis, NSAIDs for pain relief from sore joints in musculoskeletal sarcoidosis, etc. Treatments for sarcoidosis are symptomatic and not standardized, and commonly involve some kind of inflammation or pain management. Sarcoidosis can be manageable for years, often deadly if untreated, and is truly so different for every patient that experiences it, but the real issue lies in discrepancies in diagnosis due to the lack of a standard procedure for diagnosing.

On top of being hard to diagnose and case-specific to treat, sarcoidosis is also very unpredictable. A common phenomenon is a spontaneous resolution of inflammation or other symptoms, or asymptomatic cases that don't affect a person but are later discovered upon death. The phenomenon of spontaneous resolution raises the question of how many asymptomatic cases fix themselves, and whether the resolution of asymptomatic or undiagnosed cases will impact our understanding of sarcoidosis today. Spontaneous resolution is extremely hard to observe and study, as it is so unpredictable, and is a topic that will likely require additional research until scientists learn more about sarcoidosis as a whole.

Discussion

Though new research on sarcoidosis is being conducted, there is still so much more to learn about the disease and how it affects various patients. Because of how variable the disease is, there will always be a need for more research, clinical trials, and data on treatments. Many of the drugs used to treat sarcoidosis today are used for specific symptoms, not actually to treat the disease (Pasadhika, 2015).

Some of the more universal drugs prescribed for sarcoidosis patients are NSAIDs, topical steroids, and other drugs primarily used to treat inflammation or relieve pain. However, the recent classification of sarcoidosis as an autoimmune disease instead of an inflammatory disease opens the door to different drugs that can be used for treatment. As more research comes out, and scientists learn more about sarcoidosis, it can help educate both patients and doctors, and even improve sarcoidosis diagnosis in the future. As awareness and knowledge of sarcoidosis grows,

it is important to acknowledge the various manifestations of the disease, including the rarer ones, in order to develop a better understanding and prognosis for the future.

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