Sackler Journal of Medicine

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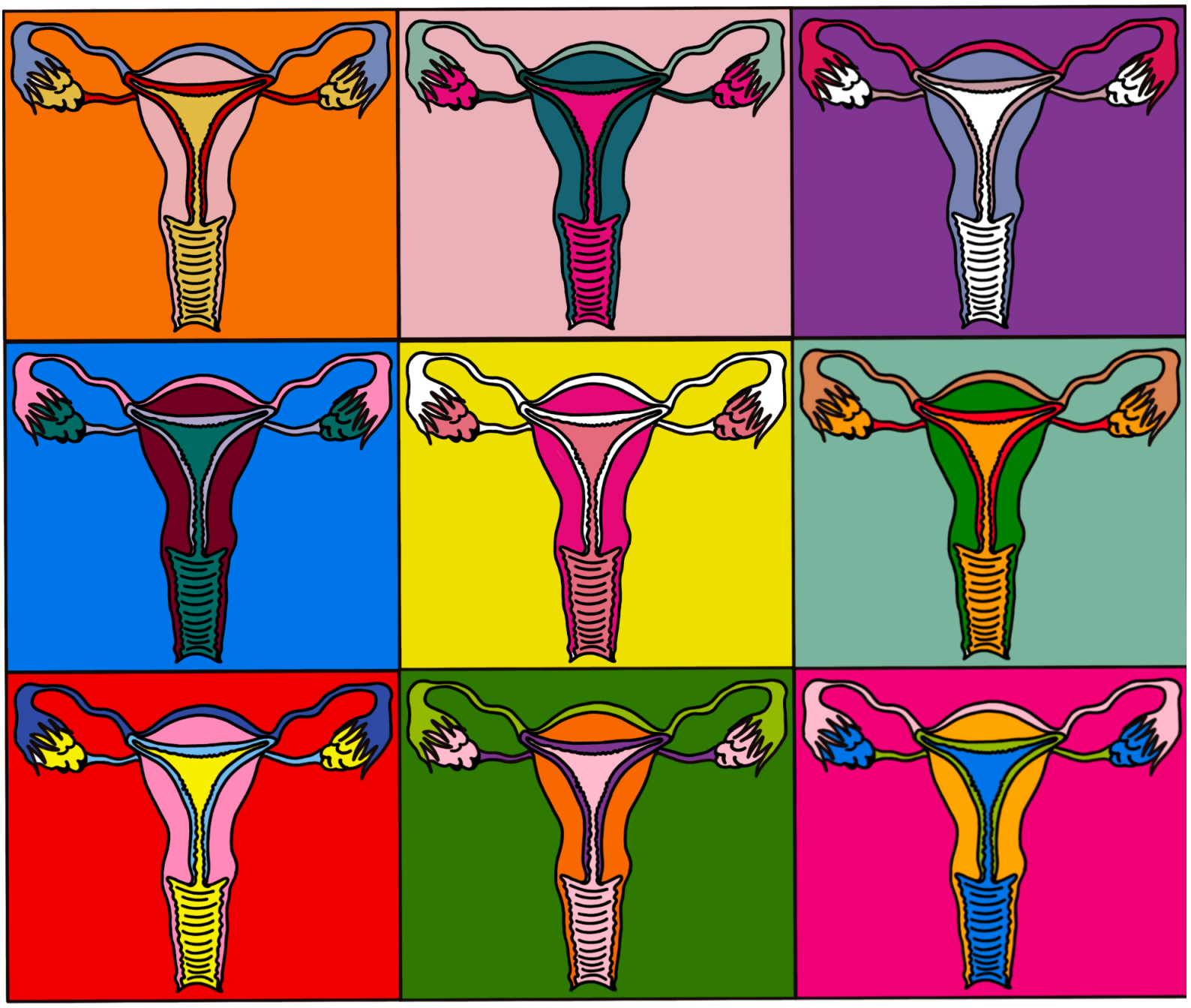

MISSION STATEMENT

What's emerging in medicine today? The Sackler Journal of Medicine – a forum where trends in medicine including translational research, the economics and policy of healthcare, and clinical experiences are explored, analyzed and discussed. SJM is a peer-reviewed journal for medical students to discuss and learn about the latest medical breakthroughs and the fundamentals of medicine.

We encourage student and physician collaboration to bring you literature reviews, case reports, original research, reflective pieces, and short commentaries on published papers. Take the opportunity to contribute your work, experiences and voice to the conversation.

SUBMISSIONS INFORMATION

Submissions from students, faculty, and individuals are welcome. For more information please visit the "Submissions" page on the Sackler Journal of Medicine website at sacklerjom.org

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COVER IMAGE

Created by Neena Carr

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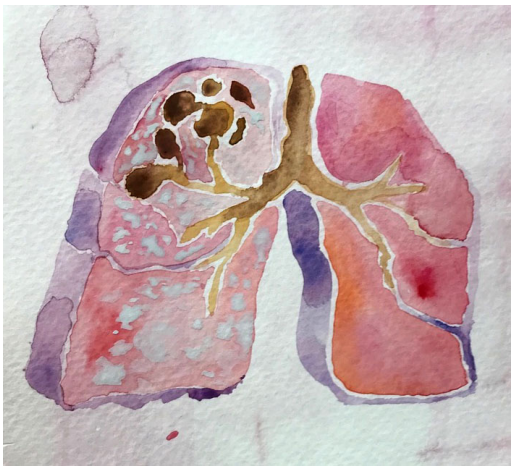

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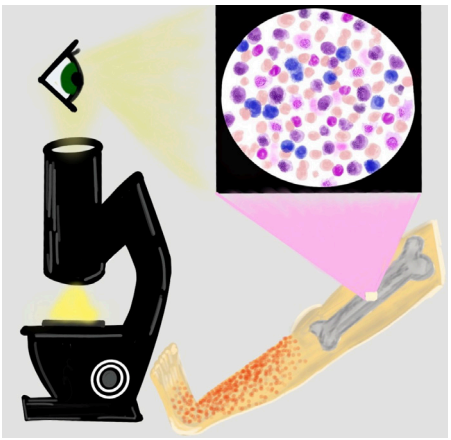

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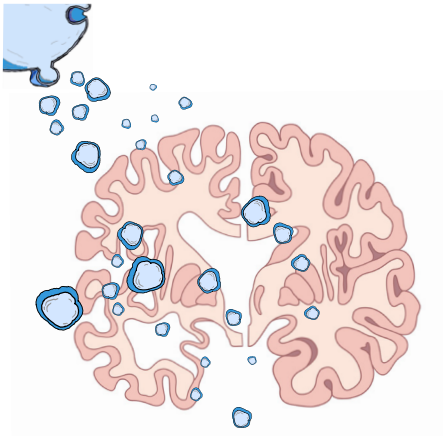

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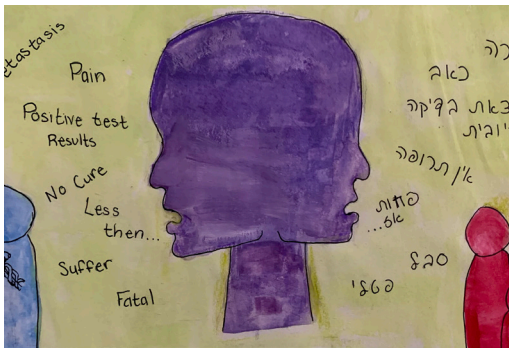

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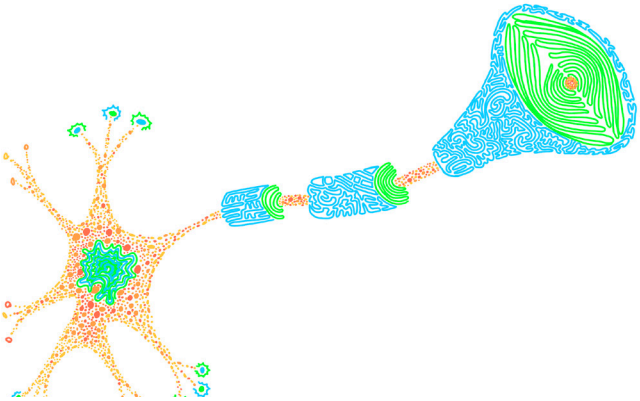

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Letter From the Editors

While the world is slowly returning to normalcy after COVID-19, the coast is anything but clear for the American and Canadian students at Sackler School of Medicine. In August 2022, the Israeli government mandated the closure of international medical graduate studies in Israel. This decision affects not only the International medical students at Tel Aviv University, but also our peers at Ben Gurion University and the Technion. While we are happy to see the Class of 2026 flourish as they begin their medical school journey, it is difficult to imagine them as the final cohort of medical graduates from our program.

Since the establishment of Sackler School of Medicine New York State/American Program at Tel Aviv University in 1976, approximately 2,000 students have graduated and gone on to contribute immensely to healthcare systems in the United States, Canada, and Israel. Despite this 46-year legacy, the decision to end the program was made in favor of Israeli medical students, who will receive the newly available positions for medical training. The decision to transform our 130 international seats into Israeli seats was made in light of the growing physician shortage in the country.

While we could discuss the arguments for and against this shift, it is inevitable that we must accept the consequences. However, it is important to recognize Sackler's impact on creating world-class physicians throughout North America and the Middle East. Dr. Barry Diner, Class of 1995, reflects on his experience at Sackler and the concrete foundation it created for his career as an emergency medicine physician. Diner noted that "living in Israel gave me the ability to grow as an individual, become more independent, and ultimately develop personal skills to be successful after graduating Sackler". Diner remains an active alumni, and will continue to advocate for the program and its graduates long after our closure.

Diner's story epitomizes the impact that Sackler has had on each of us, and our own roles as unique strings woven into the fabric of this community. A group of hard-working and compassionate individuals who push boundaries to support each other in achieving excellence, even when faced with unprecedented hurdles. While our program may close its doors, the legacy, camaraderie, and relationships it has given us will continue to flourish for years to come.

As the final few graduating classes of Sackler, our aspiring physicians are determined to make these remaining years exceptional. That is exactly what the pieces showcased in this edition embody. In this issue, we feature a diverse array of original research, reviews, opinion pieces, and artwork. These pieces transcend the norm by presenting novel science that will act as an impetus for continuously improving healthcare. You will read about reproductive technology available to the religious Jewish community, challenges with vaccination and compliance with the new Monkeypox Virus, the intricacies of Evan's Syndrome, a complex case of pediatric multiple sclerosis, and much more.

We are honored to contribute to enriching the research community at the Sackler Faculty of Medicine of Tel Aviv University and laying the foundation of scientific ingenuity for the generations to come. Thank you to all who supported and contributed to this new edition. A special recognition and thank you to all the peer reviewers, manuscript and associate editors, artists, and directorial team, whose tireless work has allowed the publication of this journal to be a success year after year. We invite you to enjoy this latest edition of the Sackler Journal of Medicine.

In Good Health,

Caroline Kaufman and Noah Igra

Co-Editors in Chief

Letter From Dr. Allen

Aaron Allen M.D.
Faculty Advisor- SJM
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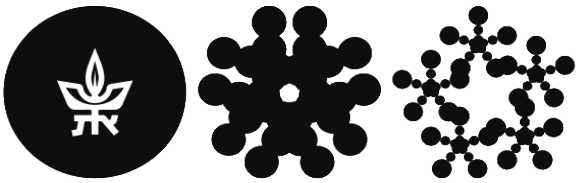

" I understood that whether you liked it or not your destiny is tied to Israel… I became a zionist"

Nathan (Anatoly Sharansky) upon his release to Israel from Russian Prison

Dear Sackler Students,

As we welcome another amazing issue of the Sackler Journal of Medicine from its student run Editorial Board and writers we are also approaching the Jewish Holiday of Chanukkah which always reminds me of the fight of the Jews of the former Soviet Union and their courageous fight for survival and quest to come to the State of Israel.

Who can not be moved by the scene described in Sharansky's book (Fear no Evil) where within the Russian Gulag he scraped together the meager rations to fashion for himself Chanukkah lights to light within his cell. He and many other during his generation of refuseniks (including my own father-in-law Yosi Shreiber) refused to allow circumstances to kill their will and desire for a better life and against all odds willed themselves to fight for a brighter tomorrow.

This of course parallels the ancient story of the Jewish Maccabees who similarly fought for survival despite overwhelming odds to establish a Jewish state despite Greek rule of the country.

This struggle for a better tomorrow despite difficult circumstances is not unique to the Jewish people but is a common motif the world over and speaks to amazing gift of the human spirit to dream and wish for a better tomorrow. Even in our own time we can see the amazing resilience of the Ukrainian people despite terrible conditions, persevering to dream of a better tomorrow.

You may ask what is the connection of these sentiments to a student run journal of medical research? Perhaps few people are so "burdened" intellectually, emotionally or even sometimes physically as the medical student trying desperately to master voluminous amounts of material and synthesize all the pieces of knowledge into a skill set that will enable them to accurately diagnose, treat and care for the sickest of patients. This is by no means an easy task!

However let's assume that student is successful in her mastery of this task . From where does the energy, drive and desire to add research and discovery to the already long list of to-do's . I believe that desire comes only from that special place within the heart of those of us that have chosen medicine to dream and will ourselves to look for a brighter tomorrow. It is an amazing ability to sacrifice personal and private goals and time for the greater good. This deserves to be celebrated and cultivated.

It is this amazing spirit that is behind the Sackler Journal of Medicine and its contributors. Students that donate of their time and effort in the hopes of forging a better tomorrow. This is truly heroic and deserves to be commended and encouraged.

So hats off to the writers, reviewers, artists and editors of SJM keep up the good work and never stop dreaming because as Sharansky wrote this is indeed your Destiny!

Professor Aaron Allen
Deputy Director
Tel Aviv University /American Program

Current Clinical Knowledge of Psilocybin Treatments - Neurology review

Yehonathan Hochberg[1], Olivia Klein[2], Roni Sharon, M.D.[1]

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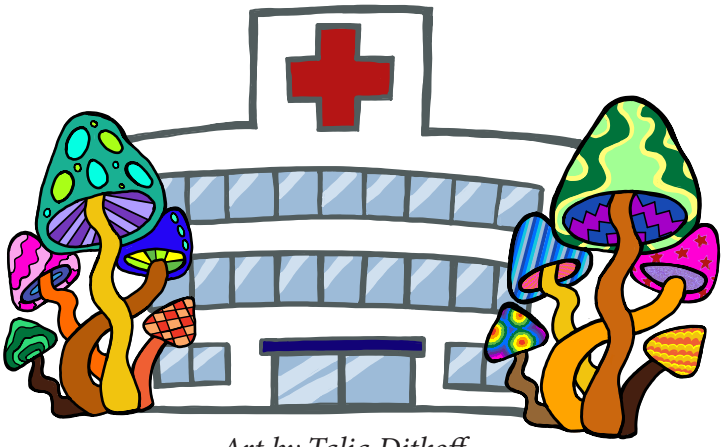

Art by Talia Ditkoff

Abstract

Background: Psilocybin is a psychoactive component found in hallucinogenic mushrooms. It has many proven therapeutic effects and is becoming a more popular treatment for a range of psychiatric disorders. Recently, research has emerged on its efficacy in treating neurological disorders such as migraines and cluster headaches.

Methods: We performed a systematic review of the current research on psilocybin's reported therapeutic effects on neurological disorders. Eligibility criteria included any human study in which participants ingested psilocybin as a treatment option for a neurological disorder. Out of the 1,418 studies that were reviewed, only six met the eligibility criteria and were included in this review. In addition, we reviewed current, ongoing studies via clinicaltrials.gov. Ten of these current studies were included in the Ongoing Research section of this review.

Results: This review included studies examining the relationship between psilocybin ingestion and headaches, such as cluster headaches and migraines. Psilocybin was deemed effective in reducing the frequency, duration, and intensity of both migraines and cluster headaches. Psilocybin was also reported as very safe, with few side effects other than mild to moderate, easily treatable headaches. It was also reported that psilocybin's effectiveness in treating these neurological disorders was unrelated to its hallucinogenic effects.

Conclusions: Overall, the results of this review indicate that psilocybin has great potential in treating neurological disorders. However, further research must be conducted to investigate these results because a large number of studies were survey based and are thus subject to various biases.

Introduction

Psilocybin is the main psychedelic component of hallucinogenic mushrooms. It was first discovered over 3,000 years ago in Mexico and was primarily used for ritualistic purposes.[1] Psilocybin was first isolated from the mushroom P. mexicana in 1958 by chemist Albert Hofmann,[2] who propagated experimental research on the compound. The research was very limited and was primarily made up of case-reports. By 1963, psychedelic research was stopped due to stricter drug regulations as a result of the Thalidomide disaster.[3] After the new regulations, psilocybin was classified as a Schedule I substance4 due to its high potential for abuse and lack of accepted medical uses.[5] Recently, however, new interest has been taken in this area as scientists are beginning to recognize the possible therapeutic effects of psilocybin. The majority of recent research on psilocybin has been conducted by Dr. Franz Vollenweider in Zürich, Switzerland because Switzerland authorizes the use of prohibited psychedelics if they are being used for drug development or scientific research.[7]

The psychedelic effects induced by psilocybin are a result of its interaction with the serotonin receptor 5-HT2A.[8] Psilocybin has been reported to have dose-dependent effects on perception, emotional state, and certain cognitive traits.[9] There have been reports of hallucinations, warped time perception, intensification of feelings, and an increase in creativity while on the drug.[10] When administration of psilocybin is done in a supportive setting, the

Publication	Method of Study	Inclusion and Exclusion criteria	Sample Size	Control Group	Findings	Side effects
Schindler et al. (2020)	Double blind placebo controlled cross over. 0.143mg/kg oral dose	Inclusion: Adults with a hisotry of migraine frequency of >2/week, free of seroergic antidepresents (≥6 weeks), free of serotonergic antiemetics (≥ 2 weeks), free of constrictive medication (≥ 5 half-lives). Exclusion criteria: hypertention, cardiac diseases, PNS diseases, substance abuse (within 3 months), Alcogol use (within 1 week), psychotic/manic disorders.	10	0.143mg/kg microcrystalline cellulose	Treatment reduced migrains from a baseline in a 2 week period after administration of psilocybin comapred to placebo but did not reduce duration, photophobia, phonophobia, nausa/vomiting. Subjects reported significantly higher 5D-ASC scores compated to placebo that did not correlate with migraine reduction.	Increase in MAP compared to placebo of 12.2 mmHg during psilocybin adminstration (p = 0.007)
Johnson et al. (2012)	Double blind placebo controlled cross over. 0, 5, 10, 20, 30 mg/70kg	inclusion: medically healthy. Exlusion: history of psychosis, alcohol, drug, and nictoine dependence (Griffiths et al, 2011)	18	lactose	significant increase in mild and moderate headache compared to placebo in a dose related fashion with a mean of 7h post drug adminstration. Headaches were not severe and disabeling and should not pose a future safety risk. Participants treated with OTC analgesics.	-
Sewell et al (2006)	Questionaire	inclusion: international classiciation of headasche disorders-2 for cluster headache as determined by medical records and that have used psilocybin or LSD for treatment. Exclusion: -	53	-	participants with episodic cluster headache and chronic cluster headache reportted either complete or partial termination of the headache	-
De Coo et al. (2018)	Questionaire	All participants must meet the ICHD-II criteria for cluster headache	613	genral papulation	Particiapnts with cluster headache use more psilocybin comapted to the general dutch population. They use it to reduce attack frequency and duration	-
Lorenzo et al. (2015)	Questionaire	Self reported cluster headache particiapnts who use illicit drugs for prophylaxis	54 (18 use psilocybin)	-	All particiapnts reported dissatisfaction with their current cluster headache treatment and opted for illicit drugs and online communities. Of the psilocybin users, 77.85 reported effective outcomes.	-
Schindler et al. (2015)	Survey	self reported cluster headache patients that was verified by a neurologist	496	-	psilocybin was found to be more effective than abortive (triptans) and preventative (verapamil) medicaitons. Psilocybin ranked highest in abortive and remission medications.	Participants reported higher side effects of prescribed medications and significantly less with illicit drugs. No specific mention of psilocybin side effects.

Table 1. Summary of publications used.

majority of the psychedelic effects encountered during the administration have been seen as positive experiences.[11] In addition to these short-term psychedelic experiences, recent findings have indicated that administering psilocybin can lead to decreases in Major Depressive Disorder,[12] possibly due to psilocybin's ability to deactivate the medial prefrontal cortex.[13] It has also shown promise in reducing tobacco smoking[14] and alcohol dependence,[15] although the exact mechanism of how this works remains unclear. Recently, psilocybin has been seen as a potential treatment for neurological disorders, including headaches,[16] Alzheimer's disease,[17] and chronic pain.[18] The purpose of this paper is to review the current research on the therapeutic effects of psilocybin on various neurological disorders.

Methods

The search was last performed on PubMed and Clinicaltrials.gov on July 29th, 2022 for the terms "psilocybin," "psilocybin and headache," and "psilocybin and neurological disorders." The eligibility criteria included all human studies that assessed psilocybin's effect on neurological disorders. This included double-blind placebo-controlled studies, questionnaire-based studies, and cross-sectional studies published in peer-reviewed journals. Animal studies, studies without an available abstract, studies not printed in English, and reviews were excluded. Due to limited research on the topic, no further limitations were placed on the trials included in this systematic review. On PubMed, 1,418 studies were found and screened based on their title, of which 19 were read in full. Of the 19, only six met the inclusion criteria (Table 1; Figure 1). On clinicaltrials.gov, a total of 113 current studies included "psilocybin," 10 of which are related to neurology disorders such as fibromyalgia, migraines, cluster headaches, pain, and phantom limb pain (Table 2). All other articles were related to other research fields that are not included in this review.

Summary of Studies:

Migraine

A double-blind, placebo-controlled, crossover study investigated the efficacy of psilocybin ad ministration on reduction in migraines.[16] Ten participants diagnosed with migraines were included in the study. All participants were required to keep a migraine journal two weeks before and after each session. Each participant received 0.143mg/kg oral psilocybin during the first experimental session and an identical placebo pill during session two. During each 6-hour session, which were separated by a two-week interval, vitals were measured at baseline and subsequently

designated intervals. The primary outcome measures included change in migraine frequency, sound sensitivity, light sensitivity, nausea/vomiting, and attack-related functional impairment. Secondary outcomes included elapsed time until next migraine, usage of migraine abortives, and overall drug and psychedelic effects. Both the primary and secondary measures were assessed two weeks after the last dosing session. Telephone follow-ups were conducted 1 day, 2 weeks, and 2 and 3 months after the final dosing session as well.

It was found that psilocybin administration resulted in a significant decrease from baseline in the number of weekly migraine days as compared to placebo ($p = 0.003$). The percentage of subjects who had at least a 25% decrease in weekly migraine days was also found to be significant as compared with placebo ($p = 0.023$). Migraine attack frequency ($p = 0.004$) and reduction in pain ($p = 0.011$) were markedly reduced compared to placebo. It was also found that the elapsed time before the onset of a second headache attack was significantly greater after psilocybin administration ($p = 0.012$). Lastly, there was a significant reduction in functional impairment ($p = 0.024$) and migraine abortive use frequency ($p = 0.014$). There was no significant decrease in the duration of headaches, sound sensitivity, nausea/vomiting, light sensitivity, or adverse effects. No positive correlation was discerned between the self-reported ratings of psychedelic effects and reduction in headaches, possibly indicating that psilocybin's efficacy in migraine reduction may not be related to its hallucinogenic effects.

Headache as Side Effect

A double-blind, cross-over study explored headaches as a potential side effect of psilocybin administration.19 A total of 18 participants, 10 females and 8 males, all deemed psychiatrically and medically healthy, were included in this experiment. Before each experiment, participants met with a study monitor to gain familiarity and develop rapport in order to reduce adverse effects later on. The first meeting was 8 hours long and subsequent meetings were 2 hours. Participants were subject to 5 testing sessions with either increasing or decreasing doses of 0, 5, 10, 20, and 30 mg/kg of psilocybin. The outcome measures of this study included both observer-rated and participant-rated drug effects during the session, self-reported headaches during or after the session, duration and severity of headaches, and use of abortive medication. The self-reported history of headaches was taken at both baseline and at one or two days post each psilocybin session.

The results indicated that participants suffered from dose-dependent headaches that increased in duration, severity, and analgesic use as the dose of psilocybin increased. Headaches were reported as mild to moderate and were not found to be related to hallucinogenic drug effect or mystical experience.

Cluster Headaches

Study 1

A survey-based study20 included 53 participants who met the International Classification of Headache Disorders-2 (ICHD-II) criteria for cluster headaches and had used either psilocybin or lysergic acid diethylamide (LSD) as a treatment method. The researchers were interested in determining how successful psilocybin and LSD were at aborting cluster attacks, ending a cluster period, and extending the remission period between attacks. It was found that psilocybin was effective in aborting an attack altogether in 22 of 26 psilocybin users, and ended a cluster period in 25 of 48 psilocybin users. Additionally, psilocybin increased the remission period between cluster headache attacks for 18 of 19 users. LSD was also deemed effective in both aborting cluster

Condition	Start Date	Study Completion date	Study ID	url
Migraine Headache	November 1, 2017	December 2022	NCT03341689	https://ClinicalTrials.gov/show/NCT03341689
Migraine Headache	August 10, 2021	July 15, 2024	NCT04218539	https://ClinicalTrials.gov/show/NCT04218539
Cluster Headache	January 21, 2020	June 1, 2022	NCT04280055	https://ClinicalTrials.gov/show/NCT04280055
Cluster Headache	November 2016	June 2023	NCT02981173	https://ClinicalTrials.gov/show/NCT02981173
Short Lasting Unilateral Neuralgiform Headache Attacks	August 11, 2021	September 30, 2022	NCT04905121	https://ClinicalTrials.gov/show/NCT04905121
Post-Traumatic Headache	March 28, 2019	July 15, 2023	NCT03806985	https://ClinicalTrials.gov/show/NCT03806985
Chronic Low-back Pain	June 2022	December 2024	NCT05351541	https://ClinicalTrials.gov/show/NCT05351541
Phantom Limb Pain	March 1, 2022	July 1, 2023	NCT05224336	https://ClinicalTrials.gov/show/NCT05224336
Fibromyalgia, Primary	August 1, 2022	July 1, 2024	NCT05068791	https://ClinicalTrials.gov/show/NCT05068791
Fibromyalgia	March 2022	May 2024	NCT05128162	https://ClinicalTrials.gov/show/NCT05128162

Table 2. Summary of current clinical trials that use psilocybin.

attacks and increasing the remission period between attacks.

Study 2

The second relevant study was an explorative cross-sectional study aimed at investigating the use of illicit drugs, including psilocybin, LSD, and heroin, to alleviate cluster headaches in the Dutch population.[21] Participants were first invited to fill out a web-based screening questionnaire, in which they had to meet the ICHD-II criteria in order to participate in the study; 634 participants were selected. Selected participants were asked to complete a questionnaire about illicit drug use and its effect on the duration and frequency of cluster headache attacks. Questionnaire results were compared to the general Dutch population statistics provided by Statistics Netherlands, which included 14,542 individuals who were separated into three groups: all people, those with chronic pain (n = 3,457), and those with headaches (n = 2,269).

Results indicated that males suffered more often from cluster headaches than females, and were more likely to take illicit drugs over women. Of the study participants, 60 cluster headache individuals reported lifetime use of psilocybin compared to only 75 in the headache subgroup of the general Dutch population statistics. A significantly larger proportion of the population diagnosed with cluster headaches use psilocybin compared to the general Dutch population ($p = 0.001$). When comparing gender, a total of 10 women and 50 men reported taking psilocybin. Only 39 of the 60 people who reported taking psilocybin filled out the questionnaires in its entirety. It was found that 56.4% of psilocybin users reported a decrease in the frequency of their cluster headache attacks and 46.2% saw a decrease in the duration of each attack, while 7.7% experienced an increase in the duration of the cluster headache attacks. The study found that only psilocybin and LSD had a significant positive influence on attack frequency. The study also concluded that the effectiveness of psilocybin is limited and requires more research. The participants in the study showed a bias toward a higher educated population due to the internet-only recruitment strategy.
In addition, the data provided by Statistics Netherlands only grouped the headache sufferers by gender and age, and other information (such as education level and income), which may have had an impact on the study's reliability, was not provided.

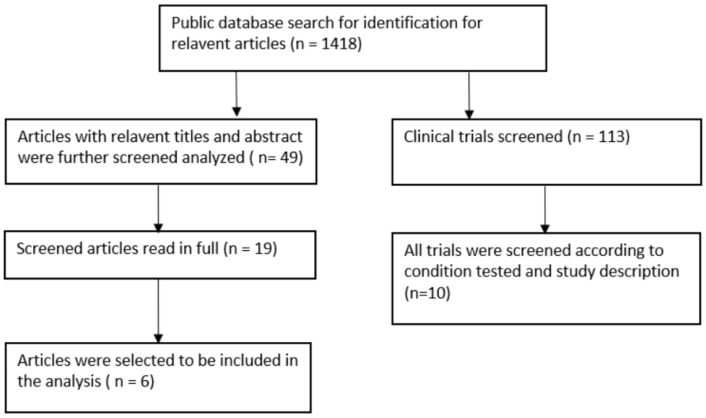

Figure 1. Flow chart of articles and trial research selection.

Study 3

A survey was sent out through an Italian self-help social media group to screen for illegal drug use as a treatment for cluster headaches.[22] The survey included questions about sociodemographics, previous recreational use of illicit substances, experience with conventional cluster headache therapies, and lifetime use of illicit substances. In order for participants' questionnaire results to be included in the study, a cluster headache diagnosis by a neurologist was required as well as no reported illicit drug use within the past year. Due to legal implications of participants' drug use, questionnaires were completed anonymously.

Results from 54 participants were included in the final results (35 men and 19 women). Of the participants included in the study, only eight attended university, and 43 had low household annual income. Forty-one patients had seen three or more different headache specialists prior to trying illicit substances, and 48 patients tried a prophylactic, conventional treatment first. The study found that out of the 18 patients who used psilocybin as their primary cluster headache prophylaxis, 14 patients reported positive treatment results. The survey found that psilocybin had similar efficacy to LSD and d-lysergic acid amide (LSA). This study had several biases and limitations. The self-help social media group, through which the survey was sent, attracts a crowd of patients that are already seeking alternative solutions compared to patients who are not in this group. In addition, self-report questionnaires are not considered the most accurate or reliable.

Study 4

A survey sent out by Clusterbusters, Inc. aimed to determine the efficacy of traditional and alternative therapies for cluster headaches.[23] The administered surveys included demographic information, headache characteristics, medication type and effectiveness. Effectiveness was rated

on a four-tier scale or through 'free-text' answer boxes. A total of 496 participants diagnosed with cluster headaches verified by a specialist or neurologist, were included for further analysis.

Results showed that 146 participants reported using psilocybin as an abortive medication and it was significantly more effective at aborting the cluster headaches than triptan pills ($p < 0.0001$) and intranasal triptan ($p < 0.0001$). Psilocybin, however, was less effective than triptan injection and high-flow oxygen. Additionally, one hundred and eighty-one participants reported trying psilocybin as a preventative medicine. It was found that psilocybin was no more effective than LSD ($p > 0.2$) or 2-bromo-lysergic acid diethylamide (BOL) ($p > 0.4$) , but was significantly more effective than methysergide ($p < 0.0001$), verapamil ($p < 0.0001$), prednisone ($p < 0.0001$), LSA ($p < 0.04$), and dimethyltryptamine ($p < 0.04$). For the results of the free-text boxes, 67 of 264 distinct responses said that psilocybin was the medication that most often shortened or aborted a cluster period. Psilocybin was identified here more times than any other medication or treatment ($p < 0.001$), with 18 respondents reporting that psilocybin was the most effective medication that led to remission from cluster headaches. The dose amount was also recorded and the survey found that 0.1 to 5gm of dried psilocybin mushroom was used for abortive purposes and 0.1 to 6gm was used for prevention. No side effects caused by psilocybin were reported.

This study was subject to several biases. The survey was only available online through particular websites, so only those who had internet access and visited the websites could participate. Additionally, these websites offered information about alternative treatment for cluster headaches, furthering potential bias for people who were already aware of alternative therapies. There were also issues with validity as the responses were subject to recall bias and different interpretations of the four levels of efficacy used to rate the medication used. Lastly, some respondents indicated that they tried many different medications, so they did not represent true, independent samples.

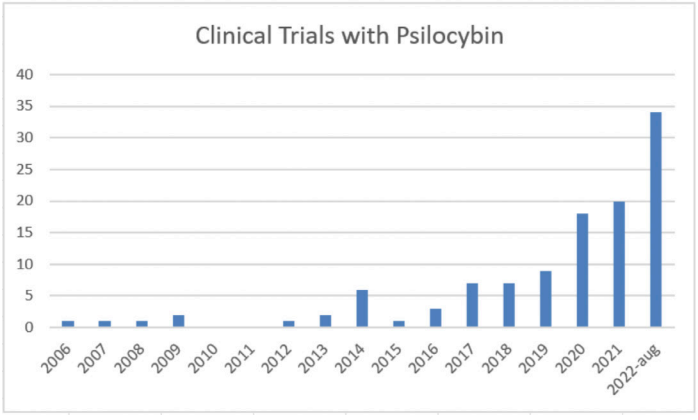

Figure 2. The exponential increase in the number of clinical studies that include psilocybin.

Ongoing research

As of August 2022, there were 113 studies that included the keyphrase "psilocybin" in the U.S. National Library of Medicine, of which 67 were in the United States. From the years 2006 to August 2022 there was a significant worldwide increase in the number of yearly clinical trials that use psilocybin (Figure 2). From the years 2006 to 2019, there were 41 trials worldwide, with 38 in 2020-2021 alone. The year 2022 saw a surge in the number of trials - 34 in the first 8 months. The majority of the studies were related to psychological and psychiatric disorders. Out of 113 trials found, only 10 were related to neurological disorders. Seventy-two were related to psychological and psychiatric disorders, with the rest classified as basic research, cancer, or other. It is worth noting that the 10 neurological trials were relatively new, with the first in 2016 with four in 2022 alone. Of the 10 trials, only one was in phase 2 (NCT05128162) while the rest were still in phase 1, indicating that this field as a whole is still in its very early research stages. This was especially evident because of the total 113 trials, 49 were in phase 2.

Discussion

Four of the six studies included in this review focused on the success of psilocybin in treating cluster headaches.[20,21,22,23] Psilocybin reportedly decreased the duration and frequency[20,21,23] of cluster headaches, and for some patients was responsible for remission of the attacks.[20,23] All of these studies were survey-based, indicating that they may lack validity and be subject to various biases. The only study that tested psilocybin's effectiveness in treating migraines16 also showed promising results for decreasing the duration of attack and reduction in pain associated with the migraine. An increase in length of time between each attack was also reported. Only one study reported that psilocybin could cause mild to moderate headaches as a side effect.[19]

Two studies reported that psilocybin was one of the most effective treatments in both prophylactic use and remission extension,[16,23] even when compared to the most widely used and approved treatments for cluster headaches and migraines. Currently, verapamil is most often used to decrease the length of an attack, while

oxygen and triptans are used to abort attacks.[23] However, most of these prophylactic medications must be taken daily and are often accompanied by unwanted side effects. Not only was psilocybin found to be just as–if not more–effective than most of these treatments, but multiple studies noted that psilocybin needed to be taken only 2-3 times per year to produce results.[20,22,23]

Three of the studies indicated that the changes in headache frequency, duration, and remission period were independent of the hallucinogenic effects often experienced by users.[16,20,22] One study even reported a negative correlation between a high mystical experience score and a decrease in migraine attacks.[16] This finding implies that the mechanism by which psilocybin acts to reduce migraines and cluster attacks is likely separate from the psychoactive effects that accompany its ingestion. It was also reported that a large portion of respondents across all surveys did not classify themselves as recreational drug users and tried psilocybin only as a potential treatment method, not to experience the psychedelic effects.

Most of the data collected and included in this review came from individuals who purchased and ingested psilocybin illegally, often against physician recommendations to avoid the drug completely.[22] However, it is important to note that none of the studies specify any alarming side effects. The most severe reported side effects were mild to moderate headache or migraine attacks that were resolved with over-the-counter medications.19 This implies that even psilocybin purchased illegally, with no standardized method to ensure its purity, may still be relatively safe as a possible treatment option. This shows promise for future experimentation and the use of psilocybin in clinical trials.

Although there has been extensive research on the effectiveness of psilocybin in treating psychological disorders, it is a relatively new treatment option for neurological disorders. Therefore, there is an absence of controlled psilocybin trials to test its effect on neurological disorders. From our research, it is clear that a substantial number of studies are retrospective and use questionnaires and social media recruiting to assess patients' experiences with psilocybin. These studies are neither controlled for patient bias nor the drug. One study[22] used online recruiting and found that only 5.6% of Italian patients who tried psilocybin to treat their condition did so based on recommendations from their physician while 94.4% found out about psilocybin from online resources. The knowledge that psilocybin can be used to treat chronic headache disorders is shared via unofficial channels that do not consider the ongoing research or possible adverse effects. Physicians should be aware of this growing online community and be open to discussing psilocybin use with their patients.

Currently, the number of studies is small and they lack diversity, but the interest in the field is growing exponentially. The evidence we have gathered thus far shows that psilocybin has potential as an effective treatment with low side effects, but more data regarding its safety and long term effects is still needed. The studies we analyzed that use online questionnaires fail to provide control groups and to effectively track data relating to negative side effects. This is probably due to the recruitment strategies, participant bias, and lack of standardization and control. Further studies from online communities should focus on the illegal psilocybin contents and purity, while clinical trials should expand on safety and long term effects on neurological disorders.

Clinical trials being conducted on primary neurological disease progression are all pain related, leading to a growing interest in the field, which will hopefully provide useful data in the future. Of the 10 neurological conditions, 6 studies were related to headaches or migraines (NCT03341689, NCT04218539, NCT04280055, NCT02981173, NCT04905121, NCT03806985) and four others were related to other pain types (NCT05351541, NCT05224336, NCT05068791, NCT05128162). There were no trials that tested direct therapy for other neurological conditions. For example, two studies on Parkinson's (NCT04932434, NCT03661125) do not focus on primary motor disorders but on depression/anxiety and psychosis respectively. The number of studies that use psilocybin has increased dramatically, but most are focused on psychiatric disorders. There is also a growing interest in cancer therapy and basic brain functioning science. Although in its early stages, the current trend shows a promising future for psilocybin therapies.

While a considerable amount of research and experimentation is still needed to ensure the safety and efficacy of psilocybin as a potential treatment for neurological disorders, this review shows promising results. It indicates that psilocybin causes minimal side effects and may be useful in reducing various forms of headaches.

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A Qualitative Review of Clinical Applications in Vagal Nerve Stimulation and its Potential Therapeutic Benefits in Acute Lung Organ Rejection and Transplantation

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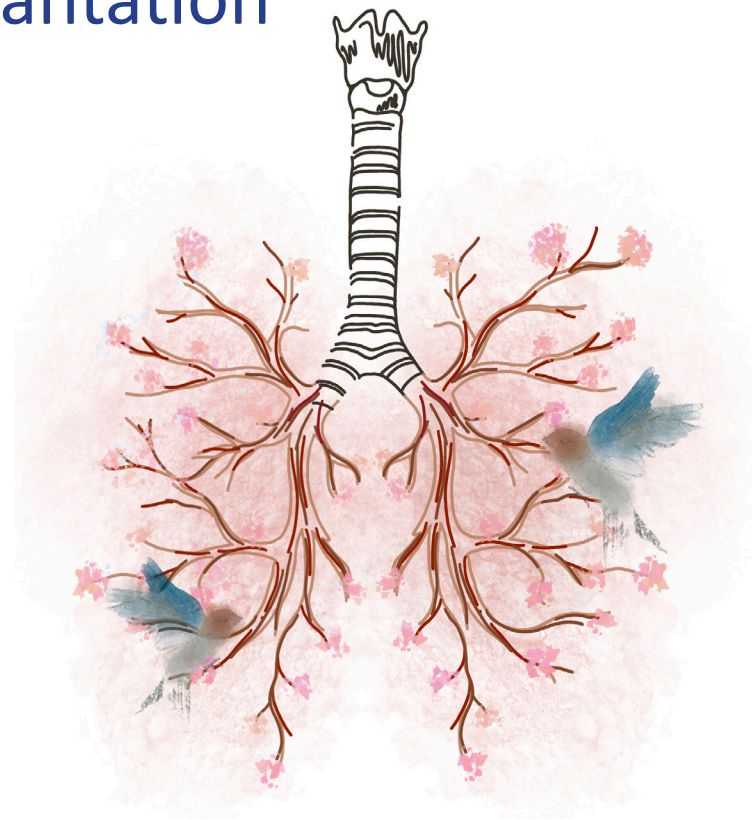
Abstract

Objective: This review intends to assess and discuss the influence of both invasive and noninvasive vagal nerve stimulation as prophylactic and supportive treatment in patients with lung transplantation rejection.
Methods: A qualitative literature review was conducted to evaluate the mechanisms, current clinical purposes, and potential therapeutic effects of invasive and noninvasive vagal nerve stimulation.
Results: The FDA has previously approved the use of vagal nerve stimulation treatment for various conditions including epilepsy, depression, migraines, and obesity. Studies have shown that vagal nerve stimulation has anti-inflammatory effects. Further studies should be conducted to broaden the awareness of the therapeutic benefit of vagal nerve stimulation in diseases including those associated with organ transplants and rejection.
Conclusions: Considering the rise in organ demand and the decline in organ supply, it is imperative to ensure transplanted organs retain function for as long as possible with the fewest number of rejections and complications. Using vagal nerve stimulation to treat organ recipients and donors can yield promising results that lead to extended patient survival and fewer complications associated with rejection management. Although further studies are required, the noninvasive nature of vagal nerve stimulation may hasten its implementation in organ rejection treatment.

Introduction

Despite advances in induction and aggressive maintenance of immunosuppression, more than a third of organ transplant recipients experience acute rejection after transplantation.[1] A high level of proinflammatory cytokines are associated with allograft rejection.[2] In serum levels of acute rejection patients, intracellular cytokines IFN-γ and TNF-α of CD4+ and CD8+ T-cells were shown to have increased.[2] New noninvasive strategies can supplement immunosuppression therapy to control the innate inflammatory responses and other injuries associated with lung rejection.



Art by Neena Carr

Numerous preclinical and emerging clinical studies have demonstrated that electrical stimulation of the cervical vagus nerve decreases serum cytokine levels, thereby reducing inflammation.[3] The vagus nerve (VN) is considered the most complex cranial nerve,[4] regulating the gastrointestinal, respiratory, cardiovascular, endocrine, autonomic and immune systems.[4] Recently, Tsaava et al demonstrated a synergistic effect between electrical vagus nerve stimulation and chronic inflammatory disorders.[3] While there is already FDA approval for using vagal nerve

stimulation (VNS) to treat depression, migraine headaches, cluster headaches, epilepsy, and obesity in the abdomen, recent evidence demonstrates that it can activate other neuroimmune circuits to reduce inflammation and cytokines in other conditions as well.[4]

In this review, we explore the prophylactic and therapeutic implications of VNS in attenuating graft vessel leukocyte infiltration and inflammation during acute postoperative organ transplantation rejection with prominent T-cell mediated immune responses. We believe that novel therapeutic options for chronic or excessive inflammatory diseases could be developed by furthering our understanding of these endogenous mechanisms that prevent or neutralize excessive proinflammatory responses.[5] Furthermore, we hope to explore how VNS may affect cytokine levels in these patients with and without the current immunosuppressive regimen.

Mechanisms by which VNS reduces cytokines and inflammatory markers. The vagus nerve is the primary structure controlling the parasympathetic nervous system.[5] Located in the medulla oblongata, the vagus nerve innervates visceral organs such as the liver and spleen, and relays information between the immune system and the central nervous system.[6] There are sensory (afferent) and motor (efferent) components to the vagus nerve. Physiological responses such as bradycardia, bronchoconstriction, increased gastric motility, and miosis have traditionally been associated with the efferent arm of the vagus nerve, while afferent fibers relay information to the brain to produce fever and other signs of illness.[6]

When the innate immune system is disrupted, proinflammatory cytokines are produced, leading to excessive or chronic inflammation.[5] The vagal neural reflex mechanism, commonly called the inflammatory reflex, connects the afferent and efferent portions of the nervous system.[5] As a consequence of tissue damage and immune response, the vagal nerve afferent pathways transmit signals to the brain stem. Once the central nervous system processes these signals, activated efferent vagal pathways inhibit immune cell production and secretion of proinflammatory cytokines, thus modulating inflammation.[7]

Inflammation reflex efferent arms are also called cholinergic anti-inflammatory pathways as acetylcholine (ACh) is the main neurotransmitter in the vagus nerve.[6] As a result of exposure to ACh, macrophages and other cytokine-producing cells become inactive.[6] Various studies have shown that ACh can suppress TNF synthesis and inhibit IL-1B, IL-8, and IL-6 release without interfering with IL-10 release, an anti-inflammatory cytokine.[6] Moreover, an increase in vagus nerve activity can activate the systemic anti-inflammatory response by communicating with the hypothalamus, the medullary reticular formation, and the locus ceruleus, which triggers adrenocorticotrophin (ACTH) production.[6]

Methods of stimulating VN

Various methods have been used to stimulate the vagus nerve through the abdomen and diaphragm in animals.[8] Human studies have almost exclusively used the VNS Therapy System to stimulate the left cervical vagus nerve.[8]

Cervical VN stimulation

In a surgical procedure, a pulse generator device is implanted subcutaneously in the left upper chest or left axilla. The electrode lead is then connected to the left mid-cervical vagus nerve through a second incision on the side of the neck.[9] Using a programming wand placed on the skin over the pulse generator, a handheld computer sets the stimulation parameters. There are four programmable parameters: current charge (mA), pulse width (microseconds), pulse frequency (Hz), and on/off duty cycle (seconds or minutes).[9] As a result, an electrical signal is sent to an organ through this subcutaneous generator, which stimulates the vagus nerve.[9] Postoperative pain and hoarseness are common complications associated with VNS. cervical surgically implanted vagus nerve stimulation.[10]

Noninvasive forms of VNS

Studies such as Mourdoukoutas et al. have stimulated the vagus nerve noninvasively by targeting the auricular branch at the concha of the outer ear or the cervical branch in the neck with transcutaneous stimulation.[11] Transcutaneous vagus nerve stimulation is typically conducted over the left branch for safety reasons as efferent fibers of the vagus nerve in the right branch control cardiac functions.[12] The cathode electrode is placed below the cheek, and the anode electrode two centimeters anterior to the cervical branch of the vagus nerve.[12] During each intervention

session, the electrical pulses typically have a pulse width of 250 seconds, a frequency of 25 Hz, and an inter-burst interval of 28 seconds. This method incites effective vagal stimulation and prevents stimulation habituation.[12] Blinding in other clinical studies has been successfully achieved with this technique and these stimulation parameters.[12]

Current clinical uses of VNS

Epilepsy
Vagal nerve stimulation was among the first neuromodulation devices approved for treating epilepsy.[13] Epilepsy treatment with VNS is acutely effective in terminating seizures. In four Class III studies, VNS reduced seizure frequency by >50% in patients with epilepsy.[14] Chronic VNS treatment also decreases the likelihood of seizure by increasing the inhibition of seizure activity[15] through reducing interictal events and desynchronizing cortical activity.[13] Despite the rarity of complete seizure freedom, VNS therapy may improve quality of life and reduce seizure frequency.[13]

Depression
The first study of VNS in adult outpatients with severe, nonpsychotic, treatment-resistant MDEs was published by Rush et al (2000).[16] Among these patients, 40% responded to treatment, including 17% who experienced complete remission.[16] A subsequent study by Elger et al. (2000) found a significant improvement in mood and seizure activity in epilepsy patients receiving VNS, suggesting further research on VNS usage for treatment of depression.[15]

According to recent neuroimaging studies, VNS can activate different brain segments, including the nucleus tractus solitarii, dorsal raphe, locus coeruleus, parabrachial area, hypothalamus, amygdala, and nucleus accumbens.[17] VNS's extensive modulation effects on these brain regions may account for multiple depression-related effects.[17] Fang et al. suggests VNS can reduce exacerbated inflammation outside the CNS and treat depression by bidirectionally connecting the brain and immune system.[17] Researchers are currently trying to identify the appropriate stimulation parameters and dosage in the context of VNS research in depression.[17]

Migraine
A number of neural structures are implicated in migraine relief, including the locus coeruleus, dorsal raphe nucleus, periaqueductal gray, ventral posteromedial nucleus, and cingulate cortex18. The pathophysiology of different headache disorders is clearly influenced by the involvement of norepinephrine, serotonin, and central sensitization in these areas.[18] Hord et al. (2003), hypothesized that VNS could reduce migraine pain by increasing thermal pain thresholds in animals.[15] The chronic use of implanted VNS was associated with headache relief in several case reports that utilized epilepsy and depression cohorts.[18] Despite these small sample sizes, these results suggest that chronic VNS can reduce migraine headache frequency and severity.[18]

Autoimmune and Inflammatory Disorders
Recent studies showing that VNS reduces inflammation in vivo have spurred preclinical research to expand the range of disorders for which VNS can be used.[19] As previously described, the cholinergic anti-inflammatory pathway (CAP) of VNS has proven effective in treating chronic inflammatory diseases like sepsis, lung injury, rheumatoid arthritis (RA), and diabetes.[19] A study by Ramkissoon et al. showed that twice daily transcutaneous auricular VNS applied to the cymba concha using a vibrotactile device reduced the expression of proinflammatory cytokines, such as TNF, IL-6, and IL-1 in RA patients.[19]

It is believed that VNS improves immune function by promoting the upregulation of the CAP, which reduces the production of proinflammatory cytokines and reactive oxygen species that contribute to autoimmune disorders.[19] Vagosympathetic nerves impact the anti-inflammatory response through cholinergic transmission exerted at the celiac ganglia and superior mesenteric ganglion of the celiac plexus via the sympathetic fibers of the splenic nerve19. This intervention results in decreased production of proinflammatory cytokines in the spleen and liver, as well as decreased TNF levels.[19]

Origin of acute transplant rejection

Organ transplantation is the gold standard for treating end-stage organ failure.[20] The main obsta-

cle to the success of these organ transplants in the first two decades is acute allograft rejection, which frequently leads to early graft failure.[21]

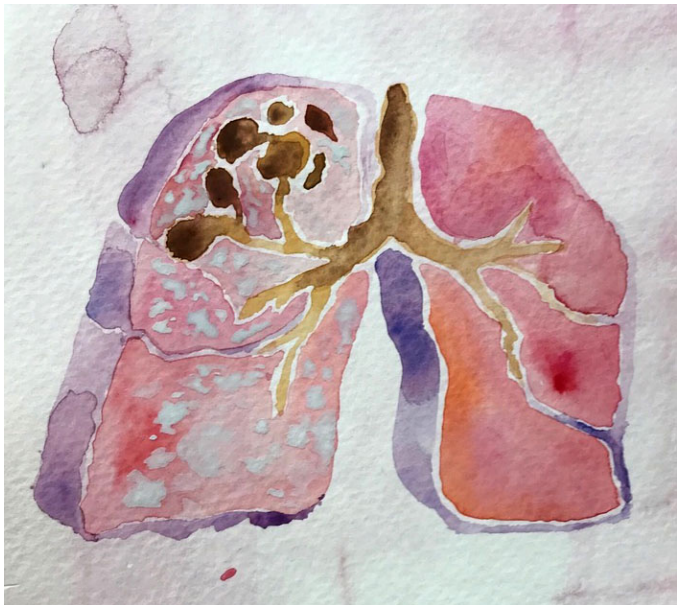
In acute transplant rejection, the immune system attacks the grafted organ within days to months after transplant.[20] As part of the rejection process, CD4+ T cells recruit a variety of effector cells that are responsible for rejection-related damage. These effector cells include CD8+ T cells, macrophages, natural killer cells, and B cells.[20] In particular, Th1 cells release IL-2 and gamma interferon, which are responsible for mediating cellular immune responses and consequently activating macrophages against allografts and xenografts. These Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13, which work to activate humoral responses through antibody production against the graft.[20]

While the past few decades have seen significant improvements in immunosuppressive drugs, long-term graft survival has not achieved the same level of success.[21] Transplant patients' life expectancies still fall short of the general population's in part because immunosuppressive drugs can increase the risk of cancer and infection.[21] There is a need for newer drugs and treatments that promote immune tolerance without causing side effects similar to those observed with current immunosuppressive drugs.[21]

Potential use of VNS in transplantation

Noninvasive VNS may have the potential to be a safe and efficient method to reduce chronic allograft loss.[22] In noninvasive VNS, the organ recipient would undergo vagal stimulation preoperatively as a prophylactic measure or during acute onset of organ rejection. Alive or deceased organ donors may also undergo VNS to preserve the life of the organ prior to retrieval.

Multiple studies have shown reduced heart rate variability in brain-dead humans and rats who have undergone VNS, suggesting a defective parasympathetic nervous system.[22] In such cases, inappropriate activity of the cholinergic anti-inflammatory pathway may exacerbate or contribute to brain death-induced inflammation in end organs.[22] Conversely, VNS in brain-dead rats led



Art by Lital Avni-Singer

to decreased expression of proinflammatory genes in peripheral donor organs and improved renal function in recipients receiving renal allografts from such donors.[22]

Another study stimulated the vagus nerve in rats that had undergone brain death. These brain-dead rats were then subjected to Quantitative PCR on all recovered organs.[23] Researchers discovered that rats exposed to VNS had lower TNFa concentrations and reduced a multitude of proinflammatory genes.[23] Moreover, vagal stimulation significantly reduced the expression of E-selectin, ITGA6, and IL1β in renal tissue.[23] Evidently, recipients who received a VNS-stimulated graft after donor brain death experienced significantly improved renal function.[23]

Hoeger et al. examined the effects of vagal stimulation on brain-dead rats in a chronic allograft setting, including kidney survival, function, and histology.[22] The study found increased survival rates and renal function as evidenced by lower serum urea levels and increased creatinine clearance.[22] There were also significant reductions in intimal arteritis, tubulitis, and persistent tubulopathy. This study demonstrated the long-lasting protective effects of vagal stimulation on brain-dead donors using a model of chronic allograft nephropathys.[22] Chronic allograft nephropathy can be reduced without causing severe side effects to the recipient in this manner.[22]

During the course of our literature review, no studies

were identified that conducted VNS directly on animal or human organ recipients. However, based on the existing literature, we believe that VNS would be associated with a fall in proinflammatory cytokines that would attenuate inflammation and leukocyte infiltration in organ recipients before and during acute rejection.

Implications of VNS

The side effect profile of VNS would vary according to whether it would be applied invasively or noninvasively. Hoarseness, throat pain, coughing, shortness of breath, and muscle pain were the most reported side effects of high vagus nerve stimulation with both modalities.[24] It is possible that symptoms would be alleviated by lowering the pulse width and frequency of stimulation, with additional benefits seen upon increased stimulation intensity.[25] Moreover, two to seven percent of cases involving the invasive modality are complicated by an infection of the subcutaneous pocket containing the VNS generator, usually with Staphylococcus aureus.[26] VNS is rarely associated with other surgical or application complications.

Conclusion

Allograft rejection, accompanied by a rise in proinflammatory cytokines, is a leading cause of morbidity and mortality after lung transplantation. Immunosuppressive treatments are routinely employed as an effective way to prevent rejection. Recent research has shown that activating the vagus nerve's efferent arm regulates cytokine production and improves survival in experimental conditions of cytokine excess, including sepsis, hemorrhagic shock, and ischemia-reperfusion injury. The cholinergic anti-inflammatory pathway can provide a localized, fast, and discrete response to inflammation by controlling the neuroimmune response and preventing excessive inflammation. The FDA has approved VNS treatment for various conditions including epilepsy, depression, migraines, and obesity. We believe that further studies should be conducted to maximize the therapeutic benefit of VNS for a broader range of diseases, including organ transplantation. Considering the rise in the demand of transplanted lungs and the decline in organ supply, it is imperative to ensure transplanted organs endure as long as possible with the fewest rejections and complications. With increased survival times for these transplanted organs, patients can expect to undergo fewer retransplants. Using VNS to treat organ recipients and donors can yield promising results that lead to longer patient survival times and fewer complications associated with current rejection measures and treatments. Although further studies are required, the noninvasive nature of VNS may help expand and accelerate its use for organ rejection treatment.

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Examining the Patterns of Monkeypox Vaccine Uptake in a High-Risk Population

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Abstract

The current monkeypox outbreak presents a unique set of vaccination challenges requiring an understanding of characteristics associated with vaccine compliance in vulnerable populations. This population-based cohort analysis of Clalit electronic health records of high-risk individuals, a majority of whom are men who have sex with men, revealed a significant increase in monkeypox vaccine administration associated with frequent STI screenings, attendance of primary healthcare clinics in an urban LGBT community, and purchase of PDE5 inhibitors. It also identified reduced compliance with low sociodemographic status and a history of vaccination non-compliance. These findings highlight the need for proactive patient and healthcare provider-oriented educational campaigns to curb vaccine hesitancy and may help direct resources toward hard-to-reach populations, hence increasing equality in vaccine enrolment.

Art by Tevyn Shadlyn

Introduction

Monkeypox virus (MPXV) is one of the many zoonotic Orthopoxvirus genus of the poxviridae family and a close relative to the variola virus (smallpox). This large double-stranded DNA virus was first identified in humans in the Democratic Republic of the Congo in 1970 and has since been considered endemic to central and western Africa.[1,2,3] Since May 2022, there has been a rapid growth in the number of new cases of MPXV outside of Africa. The recent global outbreak of human monkeypox virus infection (MPXVi) has over 80,000 confirmed laboratory cases as of November 24, 20224.

The classical clinical syndrome of monkeypox is characterized by prodromal fever and lymphadenopathy followed by a skin rash. The initial presentation has changed in the current outbreak, and cutaneous manifestations are the most common symptoms, detected in about 95% of infected patients. Most skin lesions are vesiculopustular, although a wide range of lesions have been described. Most cases are mild and self-limiting. The incubation period from exposure to development of symptoms ranges between 3-20 days, with a median of 7 days.[5] Current epidemiological data suggest that MPXVi is transmitted through sexual contact and direct contact with infectious materials.[5-7] Due to the rapid spread of the virus globally, the Centres for Disease Control and Prevention (CDC) recommend vaccinating individuals at high risk of MPXV infection.[8]

A live attenuated non-replicating vaccine for Modified Vaccinia Ankara (MVA), an Orthopoxvirus, is currently the primary vaccine approved for MPXVi by the FDA to prevent MPXVi9. Monkeypox predominantly affects young males (97.1%) at a median age of 35, with a vast majority (87.9%) identifying as men who have sex with men (MSM).[4] To contain the epidemic, the Israeli Ministry of Health (MOH) initiated an MVA vaccination campaign on July 31, 2022, prioritizing individuals at high risk for infection according to objective eligibility criteria.[10, 11]

According to the Institute of Medicine, LGBT individuals face personal and systemic barriers, such as stigma and cultural competency, which influence accessibility

to medical care. Healthcare disparities also exist from intersectional identities (e.g., racial/ethnic minorities, socioeconomic status, geographical location).[12] Since the current monkeypox outbreak disproportionately affects members of the LGBT community, more specifically MSM, such barriers may influence the effectiveness of vaccination efforts worldwide.

There is currently a global need to increase MPXV vaccination in the MSM community. A better understanding of vaccine compliance in this at-risk population could improve vaccination strategies. Therefore, our objective was to evaluate the factors associated with vaccine uptake in eligible members.

Methods

This observational, retrospective population-based cohort study was based on data obtained from the electronic medical records of Clalit Health Services (CHS), a large healthcare organization that covers approximately 52% (4.8 million) of the entire Israeli population. The study commenced on July 31, 2022, when the MVA vaccination campaign was initiated in CHS and ended on November 16, 2022.

Study participants

The study cohort included all individuals who were defined as eligible for the MVA vaccine per the Israeli MOH guidelines at the time the study commenced. The MVA eligibility criteria were: (a) males aged 18 – 42 who were dispensed HIV-PrEP since January 1, 2021, or (b) males aged 18 – 42 who were diagnosed with HIV and also were diagnosed with recorded one or more of the following STIs since January 1, 2022: active syphilis, chlamydia, or gonorrhea. The maximum age of 42 was determined based on the last year (1980) when smallpox vaccines were administered in Israel to all newborns.

The following data were extracted from CHS electronic medical records for each subject: (a) sociodemographic variables: year of birth, location of the primary healthcare clinic, sociodemographic status score (as defined in the appendix), and population sector: (b) healthcare services utilization: purchase of HIV-PrEP, purchase of PDE5 inhibitors, utilization of primary healthcare services, performance of STI tests, vaccines utilization (Covid-19, HPV, Hepatitis A, and Hepatitis B); and (c) STIs: HIV/AIDS, Treponema pallidum, Chlamydia spp. or Neisseria gonorrhea detected in urine, pharyngeal, or rectal PCR tests.

	Unvaccinated	Vaccinated	All
Total N	965	1060	2025
	N (%)	N (%)	N (%)
Sociodemographic variables			
Age, mean (SD)	33.7 (5.7)	34.1 (4.8)	33.9 (5.3)
Birth Country – Israel	739 (76.6)	961 (90.7)	1700 (84.0)
Tel-Aviv district	424 (43.9)	806 (76.0)	1230 (60.7)
Sociodemographic status score below the median	476 (49.3)	340 (32.1)	816 (40.3)
Population sector- minority	56 (5.8)	22 (2.1)	78 (3.9)
Clinical risk factors			
History of HIV/AIDS	521 (54)	149 (14.1)	670 (33.1)
History of Syphilis infection	209 (21.7)	244 (23.0)	453 (22.4)
Recent Syphilis infection	32 (3.3)	65 (6.1)	97 (4.8)
Recent STI in urinary test	31 (3.2)	70 (6.6)	101 (5.0)
Recent STI in pharyngeal test	58 (6.0)	164 (15.5)	222 (11.0)
Recent STI in rectal test	64 (6.6)	166 (15.7)	230 (11.4)
Any recent STI	122 (12.6)	308 (29.1)	430 (21.2)
Healthcare services utilization			
Purchase of HIV-PrEP - purchased 1-2 prescriptions from 01/2021 to 08/2022	132 (13.7)	173 (16.3)	305 (15.1)
Purchase of HIV-PrEP - purchased 3 or more prescriptions from 01/2021 to 08/2022	285 (29.5)	667 (62.9)	952 (47.0)
Purchase of PDE5-inhibitors	114 (11.8)	206 (19.4)	320 (15.8)
Low utilization of primary healthcare services*	474 (49.1)	398 (37.5)	872 (43.1)
Vaccine utilization			
Not vaccinated for HPV	759 (78.7)	591 (55.8)	1350 (66.7)
Not vaccinated for COVID-19	131 (13.6)	45 (4.2)	176 (8.7)
Not vaccinated for Hepatitis A	724 (75.0)	667 (62.9)	1391 (68.7)
Not vaccinated for Hepatitis B	530 (54.9)	507 (47.8)	1037 (51.2)
STI tests			
Tested for Syphilis more than once**	447 (46.3)	845 (79.7)	1292 (63.8)
Tested for STI in urine more than once**	390 (40.4)	833 (78.6)	1223 (60.4)
Tested for STI in pharyngeal sample more than once**	249 (25.8)	667 (62.9)	916 (45.2)
Tested for STI in rectal sample more than once**	238 (24.7)	660 (62.3)	898 (44.3)
Tested for any STI***	674 (69.8)	998 (94.2)	1672 (82.6)

***test performed from January 20222 until June 2022*
****any urine, rectal or pharyngeal STI test since January 2022*
Table 1 –Characteristics of vaccinated versus unvaccinated study participants

This observational cohort study is based on routine data from electronic medical records from CHS and includes sociodemographic and clinical information. The study was approved by the CHS Institutional Ethics and Data Utilization Committees.

Statistical analysis

Descriptive statistics were used to characterize the study participants, including those who received and did not receive the MVA vaccine.

The location of the primary healthcare clinics was classified as Tel Aviv versus other districts, the population sector was classified as minorities (including Arabs and Ultraorthodox Jews) versus the rest of the population, and the sociodemographic status

	Univariable models results	Multivariable model results
	HR (95% CI)	HR (95% CI)
Sociodemographic variables		
Birth Country - Israel	**2.29 [1.86, 2.81]**	1.21 [0.98, 1.50]
Tel-Aviv district	**2.93 [2.54, 3.37]**	**1.77 [1.51, 2.07]**
Population sector- minority	**0.43 [0.28, 0.64]**	0.71 [0.46, 1.10]
Sociodemographic status score below median	**0.60 [0.52, 0.68]**	**0.82 [0.72, 0.93]**
Clinical risk factors		
History of HIV/AIDS	**0.23 [0.19, 0.27]**	**0.48 [0.37, 0.63]**
History of Syphilis infection	1.06 [0.92, 1.22]	
Recent Syphilis infection	**1.47 [1.14, 1.89]**	1.05 [0.82, 1.36]
Recent STI in urinary test	1.59 [1.25, 2.03]	
Recent STI in pharyngeal test	2.06 [1.75, 2.44]	
Recent STI in rectal test	1.83 [1.55, 2.16]	
Any recent STI	**2.00 [1.75, 2.29]**	1.10 [0.95, 1.27]
Healthcare services utilization		
Purchase of HIV-PrEP		
Did not purchase PrEP (ref)	1.00	1.00
Purchased 1-2 prescriptions	**3.45 [2.00, 2.99]**	1.08 [0.84, 1.40]
Purchased 3 or more	**3.68 [3.16, 4.29]**	**1.32 [1.05, 1.65]**
Purchase of PDE5-inhibitors	**1.53 [1.32, 1.78]**	**1.20 [1.02, 1.39]**
Low utilization of primary healthcare services*	**0.71 [0.63, 0.81]**	0.97 [0.85, 1.10]
Vaccines utilization		
Not vaccinated for HPV	**0.49 [0.44, 0.56]**	**0.72 [0.63, 0.81]**
Not vaccinated for Covid-19	**0.37 [0.27, 0.49]**	**0.50 [0.37, 0.68]**
Not vaccinated for Hepatitis A	**0.67 [0.59, 0.76]**	0.90 [0.79, 1.03]
Not vaccinated for Hepatitis B	**0.81 [0.72, 0.92]**	1.10 [0.97, 1.25]
STI tests		
Tested for Syphilis more than once	**3.11 [2.67, 3.61]**	0.80 [0.63, 1.03]
Took STI urine test more than once	**3.57 [3.08, 4.14]**	**1.39 [1.10, 1.77]**
Took STI pharyngeal test more than once	**3.10 [2.74, 3.52]**	1.10 [0.78, 1.55]
Took STI rectal test more than once	**3.15 [2.78, 3.58]**	1.24 [0.88, 1.74]

Table 2- Univariate and multivariate Cox proportional hazards models for MPXV vaccine uptake

score was classified as above or below the median in the study population. Positive PCR results for Chlamydia spp. or Neisseria gonorrhea were grouped according to the type of sample obtained (urine, pharyngeal, or rectal).

In the univariable analysis, we used Cox proportional hazards models with the MVA vaccine as the outcome and the date of vaccine uptake as the time variable to estimate hazard ratios. All variables significantly associated with the outcome at $p<0.05$ were entered into the multivariate Cox proportional hazard model. Analyses were conducted in R statistical software version 4.0.1 (R Project for Statistical Computing). All reported p-values are two-tailed.

Results

Study participants

Out of 4.8 million CHS members, 2,025 met the study eligibility criteria (4.22 per 10,000 population). During the study period, 1060 (52%) participants received the MVA vaccine. The mean age of all study participants was 34 years of age, and 60.7% were registered to primary healthcare clinics in the Tel Aviv district. Of the study participants, 33.1% had HIV/Aids, 47.0% purchased HIV-PrEP at least three times since January 2021, 82.6% took at least one test for STI since January 2021, and 21.2% tested positive for at least one STI (Treponema pallidum, Chlamydia spp. or Neisseria gonorrhea) since January 2022. The stratified characteristics of participants who received and did not receive the MVA vaccine are detailed in Table 1.

Healthcare services utilization para
meters were strongly associated with MVA vaccine compliance. Performing more than one urine test since January 2021 was associated with a higher likelihood of receiving the MVA vaccine (HR= 1.39, 95% Confidence Interval (CI): 1.10- 1.77). Previous non-compliance with recommended vaccines was associated with lower chances for MVA vaccine compliance: subjects who did not receive the COVID-19 vaccine were 50% less likely (HR: 0.50, 95%CI: 0.37- 0.68), and those who did not receive the HPV vaccinations were 28% less likely (0.72, 95%CI: 0.63-0.81) to comply with the MVA vaccine. Recent purchase of HIV-PrEP (3 purchases or more in six months) and purchase of PDE5-inhibitors, introduced as an indicator for possible risky sexual behavior, were associated with higher chances of MVA vaccine compliance (HR=1.32, 95%CI: 1.05- 1.65 and HR=1.20, 95%CI: 1.02- 1.39, respectively).

Some sociodemographic characteristics were also associated with vaccine compliance. Attendance of primary healthcare clinics in the Tel Aviv district was associated with higher MVA vaccine compliance (HR=1.77, 95%CI: 1.51-2.07), while a sociodemographic score below the median was associated with lower vaccine compliance (HR=0.82, 95%CI: 0.72-0.93).

Individuals with a history of HIV/AIDS were less likely to comply with receiving the MVA vaccine in our study

cohort (HR=0.48, 95%CI: 0.37-0.63). Recent STIs were not associated with vaccine uptake.
Table 2 details each independent variable's association with MVA vaccine compliance and results from the multivariable Cox proportional hazard model for MVA vaccine compliance.

Discussion

This study identified characteristics associated with MVA vaccine compliance in a high-risk, vaccine-eligible cohort. Attendance to a primary healthcare clinic in the Tel Aviv district, repeated STI screening, and a recent purchase of HIV-PrEP or PDE5 inhibitors were associated with higher vaccine compliance. In contrast, previous non-compliance with recommended vaccines, low sociodemographic status, and history of HIV were associated with lower compliance.
Some factors associated with vaccine compliance were also associated with increased risk for MPXVi before the vaccination campaign was launched[13]: attendance to a primary healthcare clinic in the Tel Aviv district and purchase of HIV-PrEP or PDE5 inhibitors. Thus, vaccine compliance may reflect, in part, the individuals' perceived risk for MPXVi.
The higher vaccine compliance in the Tel Aviv district was reflected in other studies showing higher HPV vaccination and healthcare utilization among MSM in other metropolitan areas.[14] In addition to a possible higher perceived risk for infection, healthcare utilization of sexual minorities was influenced by demographic characteristics and community connectedness.[15] Another factor that may contribute to higher compliance is physicians' endorsement. For example, a study showed HPV vaccine compliance among MSM to be 83% when vaccination was recommended by a healthcare provider, compared to only 5% when no such recommendation was précised.[16–18] The main LGBT clinics and physicians of CHS are located in the Tel Aviv district and were likely to recommend the MVA vaccine to their patients.
In our study, participants who used HIV-PrEP were more likely to be vaccinated, particularly those who purchased three or more prescriptions within six months. This further supports a correlation between healthcare utilization and patients' perceived risk with vaccine uptake, as demonstrated in previous studies regarding HPV vaccine uptake in HIV-PrEP users.[7,19] Having HIV was found to be associated with lower MVA vaccine compliance within our cohort. It should be noted that HIV was an eligibility criterion for the MVA vaccine as defined by the Israeli MOH. However, living with HIV may not be criterion sensitive enough to identify MSM since it represents a varied population, including persons who immigrated to Israel from countries endemic to HIV. Hence, our cohort is limited in identifying MSM living with HIV.
Participants in our study who obtained PDE 5 inhibitors prescriptions had a higher likelihood of MVA vaccine uptake. Utilization of PDE5 inhibitors within the MSM community has been correlated with riskier sexual behavior, such as having multiple sexual partners, condomless anal intercourse, illicit drug use, and drug-enhanced sexual practices ("chemsex").[20,21] PDE5 inhibitor use may therefore mirror risky sexual behavior.
Participants with more than one STI screening test within the study period had a markedly higher likelihood of MVA vaccination. This is reflected in other studies, where HPV vaccine uptake for MSM increased with increased health-seeking behavior, including STI screening.[16,22]
Individuals who did not comply with other recommended vaccines (HPV and COVID-19) were less likely to receive the MVA vaccine in our study. Similarly to the current MPXV outbreak, both HPV and Covid-19 infections were shown to disproportionately affect LGBT+ individuals.[18,23] Other studies echo this trend, showing that MSM previously vaccinated for hepatitis A were more likely to acquire HPV and COVID-19 vaccinations.[19,24,25]
A lower sociodemographic score was associated with a lower likelihood of MVA vaccination. Similarly, surveys found that MSM experiencing financial hardships or living in rural areas were less likely to comply with other vaccines like the COVID-19 and HPV vaccines.[14,19]

Policy Implications

MVA vaccines to prevent MPXVi are currently recommended for MSM in most countries.[26] This recommendation creates additional barriers to vaccination as it requires disclosure of one's sexual identity and behavior.[16,27] Additional barriers to LGBT vaccination include affordability, accessibility, and trust in the healthcare system, which has been strained by a history of marginalization and systemic discrimination toward the LGBT community. [23]
Well-structured public health strategies, including targeted campaigns and patient education, are needed to disseminate reliable information about MPXV immunization and curb vaccine hesitancy. Educational campaigns promoting vaccine enrollment should include both patient and medical provider-oriented campaigns. Patient-directed social media campaigns can be used to target specific at-risk

This retrospective analysis of medical records identified factors associated with MVA vaccine uptake. This may help direct resources towards hard-to-reach populations, hence increasing vaccine enrollment equality.

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Clinical Manifestations of Evan's Syndrome Secondary to a Myeloproliferative Malignancy

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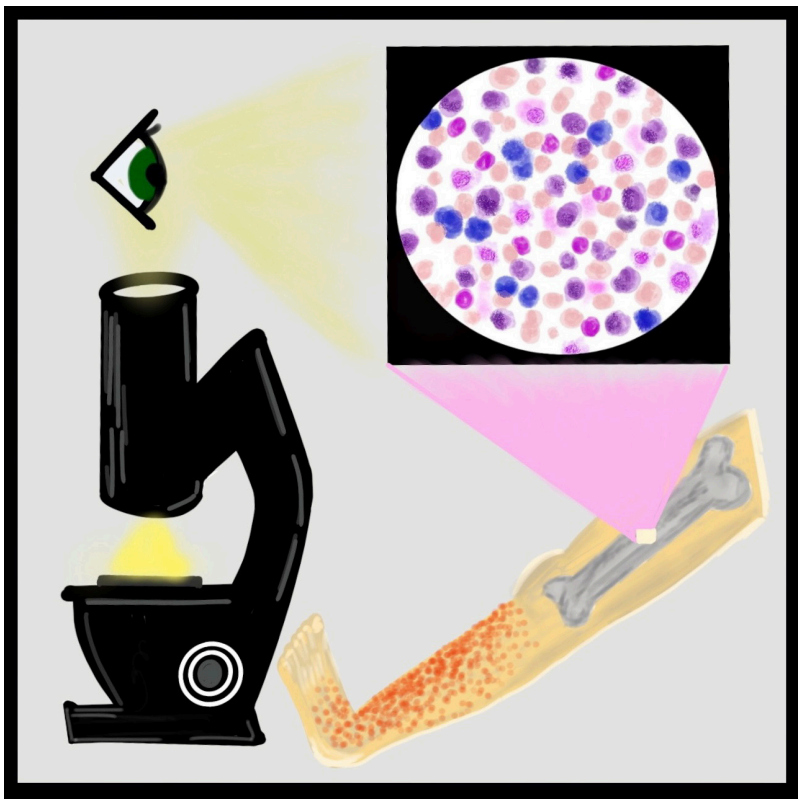
Abstract

Evans syndrome (ES), a bicytopenia of autoimmune hemolytic anemia and immune thrombocytopenic purpura, is a rare and severe disease, especially in adults. ES can occur secondary to lymphoproliferative malignancies. The clinical picture of adult-onset ES and its sudden development from malignancy is rare. Here, we present a case of a patient diagnosed with ES in late adulthood as a manifestation of splenic marginal zone lymphoma, a non-Hodgkin's lymphoma. ES is a diagnosis of exclusion; thus, it requires strong clinical recognition. The development of ES and its relation to malignancies need to be better documented. We hope that by sharing this case of ES in late adulthood secondary to malignancy, we can raise awareness about ES in the scientific community.



Art by Ariela Haimovich

Introduction:

Immune thrombocytopenic purpura (ITP) is an acquired thrombocytopenia caused by autoantibodies against platelet antigens and a common cause of thrombocytopenia in asymptomatic adults.[1] Since ITP is a diagnosis of exclusion, it is challenging to diagnose.[1] The lack of a sensitive or specific diagnostic test for ITP and the many other potential overlooked causes of isolated thrombocytopenia, both contribute to the challenges in diagnosing ITP. Identifying whether thrombocytopenia is primary (idiopathic) or secondary to an underlying condition (e.g. drug-induced thrombocytopenia, hereditary thrombocytopenia, infection-induced thrombocytopenia, malignancy) is another concern that impacts potential treatment.[2] Pinpointing the cause of the thrombocytopenia is vital to patient management. For instance, drug-induced thrombocytopenia would improve upon cessation of the offending drug while idiopathic ITP requires immunosuppressive therapy.

High Yield Learning Points

- **Immune thrombocytopenic purpura (ITP), known as idiopathic thrombocytopenic purpura or immune thrombocytopenia, is a type of thrombocytopenic purpura defined as an isolated low platelet count with normal bone marrow in the absence of other causes of low platelets.**
- **Autoimmune hemolytic anemia (AIHA) occurs when antibodies directed against the person's red blood cells (RBCs) cause them to burst (lyse), leading to an insufficient number of oxygen-carrying red blood cells in the circulation.**
- **Evans syndrome is an autoimmune disease in which an individual's immune system attacks thier red blood cells and platelets. The syndrome can include immune neutropenia.**

Evans syndrome (ES) is a rare autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and ITP, and/or immune neutropenia.[3,4,5] Although the definition of ES in many past studies has been restricted to red blood cell and platelet destruction, the diagnosis can be any combination of ITP, AIHA, autoimmune neutropenia, or immune pancytopenia. Studies have shown that ES as a whole is more resistant to immunosuppressive therapies than a diagnosis of either ITP or AIHA alone. Thus, patients with ES have a worse prognosis.[3,5]

Autoimmune disorders like ES are often a manifestation of lymphoproliferative disorders. However, the clinical features of ES are not well understood due to its rare occurrence. In addition, the relationship between ES and malignancies has not been thoroughly documented. This case report presents a patient who developed ES that was found to be secondary to Non-Hodgkin's Lymphoma.

Case Presentation:

An 83-year-old woman with a history of monoclonal gammopathy of undetermined significance (MGUS) and Coombs-positive AIHA presented to the internal medicine ward at Sourasky Medical Center with a 2-month history of weakness, fatigue, increased sleep, and sore throat. In the week prior to her admission, she had an episode of melena and petechiae which appeared on her lower eyelid, along with purpura on the dorsal side of her lower legs. In the emergency department, she presented with hematemesis and had blood removed by endoscopic vacuum therapy.

Her vitals on admission showed signs of hemorrhagic shock. She was hypotensive with a blood pressure of 81/69 mmHg, mildly tachycardic, and afebrile, with a normal O2 saturation. Her labs showed normocytic normochromic anemia with a severely low hemoglobin (3.9g/dL), in-range reticulocyte index, severe thrombocytopenia with a platelet count of 7000/microliter, leukocytosis with lymphocytosis of 7000/microliter, and an elevated LDH. Her coagulation profile showed elevated D-dimer (850 ng/mL) and INR (1.21), with low fibrinogen (168 mg/dL), indicating possible DIC. However, her blood smear showed spherocytes, likely from the AIHA, but was negative for schistocytes or blasts. On imaging, her chest x-ray showed a right lower lobe (RLL) consolidation, and cerebral CT was negative for hemorrhage. She denied taking any medications or supplements.

To stabilize her, she was transfused with two packs of red blood cells, 12 packs of platelets, hydrocortisone for AIHA, and ceftriaxone plus azithromycin to cover the possibility of typical or atypical pneumonia seen on chest X-ray.
In summary, the patient presented with severe thrombocytopenia and normocytic normochromic anemia with signs of hemolysis and bone marrow suppression. She also presented with symptoms of a respiratory tract infection. Her thrombocytopenia likely led to an upper GI bleed, causing the melena and hematemesis, which further worsened her anemia and developed into a picture of hemorrhagic shock.

We will now discuss the process of arriving at a diagnosis for the patient. Her ISTH (the International Society of Thrombosis and Hemostasis) score for DIC did not meet the criteria (fibrinogen<100 and INR<1.3), making DIC an unlikely diagnosis. A subsequent full-body CT showed splenomegaly and that her RLL lesion was most likely a benign hemangioma and otherwise unremarkable. Blood cultures and viral panels were negative for any current infections, including the common infectious causes of thrombocytopenia such as Hepatitis B and C, CMV, HIV, Parvovirus, and Mycoplasma. She was positive for anti-Ro and ANA antibodies, but had no clinical symptoms of dermatomyositis or polymyositis. With no other potential causes of thrombocytopenia, she was diagnosed with ITP and thus ES because of her history of AIHA.

In light of ES and her unexplained lymphocytosis, she underwent a workup for lymphoproliferative cancer via bone marrow aspiration under the suspicion of a lymphoma-causing hematologic autoimmune phenomenon. The results returned positive for CD20, a marker for splenic marginal zone lymphoma (SMZL). The combination of splenomegaly, lymphocytosis, bicytopenia, autoimmune manifestations of AIHA and ITP, the monoclonal elevated IgM (MGUS), and positive CD20, led to the diagnosis of SMZL.

Discussion

In this report, we present a case of a patient who developed ES secondary to Non-Hodgkin's Lymphoma. ES should be kept in the differential when lab parameters present a low platelet count with low hemoglobin

levels.[3,5] Similarly to the diagnosis of ITP, ES is also a diagnosis of exclusion and can only be made after ruling out all other possible diagnoses. Specifically, a diagnosis of ES may be made when AIHA and ITP occur in the same patient, even if not at the same time. ES can be life-threatening, with an overall mortality rate of approximately 20%. It is associated with a high rate of severe infections and thrombosis.[2] Concerning survival, the severity of anemia at diagnosis is a main predictor of mortality. This is similar to what has been reported in primary AIHA, where each gram of Hb reduction yielded a 7% greater risk of relapse.[3] Moreover, all-cause mortality was higher in patients with ES than in the general population and the proportion of deaths resulting from bleeding was greater in ES than in isolated ITP.[5]

A prospective international registry for adult ES would allow the collection of more precise data on disease course, treatment, and complications, as forms of adult ES are often excluded from clinical trials for ITP and AIHA.[2] Therefore, a specific approach is lacking. In conclusion, adult ES is a rare and severe disease requiring high clinical awareness, accurate diagnosis to assess secondary forms, and prompt treatment. Therapeutic strategies should consider the risk of infection, thrombosis, relapse, and prophylactic measurements for those complications.

ES in children more commonly has a better prognosis, while adult-onset is both more severe and rare. In adult ES, the workup should exclude lymphoproliferative syndromes, as they can present with similar symptoms and also cause ES. The specific diagnostic tests and procedures used to evaluate and diagnose ES may vary depending on the individual case, but they may include physical examination, blood tests, imaging studies, and biopsy. Even rarer associations, such as primary immunodeficiencies, should be extensively investigated and excluded (by a history of recurrent infections, immunoglobulin level evaluation, lymphocyte subpopulations, and genetic testing).[2,3,5]
Here we present a case of a woman who developed ES as an adult. We offer this case to raise awareness that ES can present in late adulthood secondary to malignancy.

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COMMENTARY/REVIEW

Extracellular Vesicles: Biogenesis, Function, and Role in the Progression of Alzheimer's Disease

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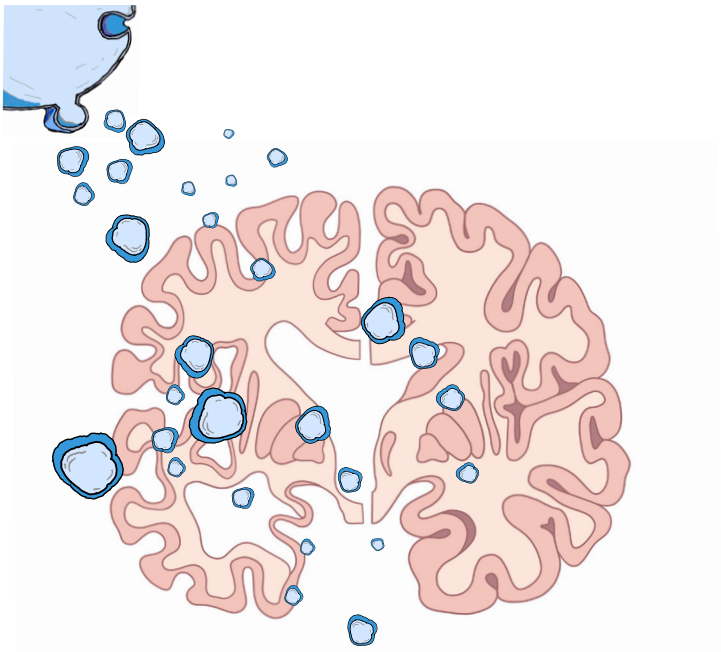

Art by Talia Mandell

Abstract

Extracellular vesicles and microRNAs are novel potential therapeutic strategies for the treatment and prevention of diseases. This review aims to summarize the current understanding of the role of extracellular vesicles in cell-to-cell communication with the aim of utilizing these mechanisms in the development of new treatment strategies. It covers various types of extracellular vesicles, including exosomes, microvesicles, and apoptotic bodies, and their mechanisms of release and uptake, with a focus on the potential involvement of microRNAs in the pathogenesis of diseases such as Alzheimer's disease.

Biogenesis of Extracellular Vesicles

Extracellular vesicles are membrane-bound vesicles implicated in cell-cell communication and have been found to circulate through blood, urine, and lymph.[1,2] Although the nomenclature, composition, and biogenesis of extracellular vesicles are highly debated today, they have been implicated in diabetes, liver disease, Alzheimer's disease, and cancer.[3,4,5] Currently, novel treatments using extracellular vesicles as possible vessels for drug delivery are being explored.[6,7]

Since extracellular vesicles are released in all tissues, their impacts on disease are not only diverse but also difficult to isolate, making them challenging to study but fascinating nonetheless.[6]

An extracellular vesicle is an umbrella term encompassing microvesicles, apoptotic bodies, and perhaps most elusive exosomes.[2] Healthy cells release both exosomes and microvesicles (Fig. 1). Exosomes are formed within the endosomal network.[9] Late endosomes are characterized by the presence of many small multivesicular bodies that can be released through fusion with the plasma membrane, where they become exosomes. In contrast, microvesicles, also known as ectosomes, are formed from outward budding of the plasma membrane.[9] Although the compositions of microvesicles and exosomes differ, their dissimilar biogenesis remain their primary differentiating factor.[2,7] Healthy and cancerous cells can release apoptotic bodies while under stress. Apoptosis begins with membrane blebbing and chromatin condensation and eventually progresses to cell and nuclear fragmentation (Fig. 1).[2] During the final stages of apoptosis, apoptotic bodies are released containing damaged organelles and proteins. The most considerable similarity among apoptotic bodies, microvesicles, and exosomes is their unique role as a critical signaling platform.[4]

Extracellular Vesicles as Key Signaling Platforms

Extracellular vesicles are not simply a mechanism to reject damaged cellular components, rather there is increasing evidence that they have essential roles in intracellular communication.[1,3,4,5,10,11] Typical cellular communication pathways involve a cell secreting a protein through the secretory pathway or taking up small molecules through transport channels.[6] However, extracellular vesicles are unique in that they contain fragments of the cell and are released as free vesicles into extracellular space.[11,13] There are many advantages and disadvantages to targeting extracellular vesicles as therapeutics or biomarkers for disease. On

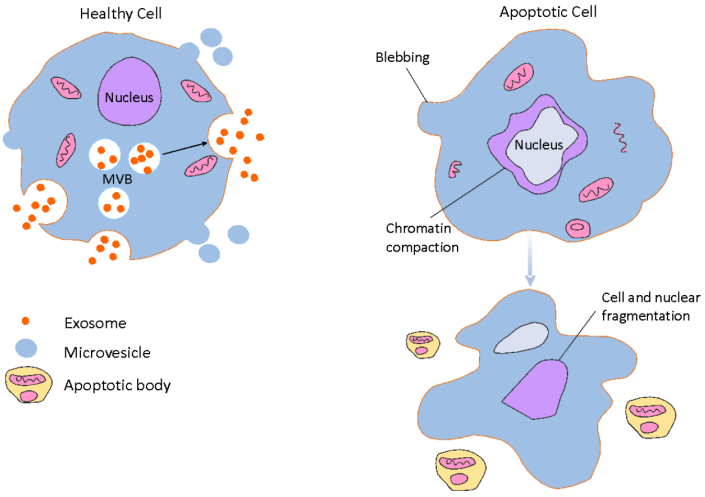

Figure 1. *Biogenesis of microvesicles, apoptotic bodies, and exosomes. Microvesicles and exosomes are released from healthy cells through fission and fusion with the plasma membrane, respectively. Apoptotic bodies are released at the final stages of apoptosis.*

the one hand, they are highly stable due to their lipid membranes, which are enriched in cholesterol and sphingomyelin, making them advantageous for long-term drug delivery.[9] However, isolation and purification techniques for extracellular research are still poorly established.[11] It is challenging to isolate exosomes from bodily fluids as their size overlaps with microvesicles. Ultracentrifugation, a long-standing method for separating these vesicles, is slowly being replaced with new microfluidic devices that use polymer-lined micro-sized channels to sort exosomes with a high level of purity.[11]

Extracellular vesicles protect cargo within their membranes and can deliver cargo to specific cell-types through various ligand interactions. A study by Peinado et al. revealed that metastatic melanoma-derived exosomes "educate" bone marrow progenitor cells by upregulating MET oncoprotein. Their research further supports the astonishing ability of exosomes to alter cells in a durable manner suggesting that exosomes may regulate genetic or epigenetic changes within cells.[14] Borges et al. determined that the activation of fibroblasts in part causes renal fibrosis due to the release of exosomal TGF-β mRNA by injured tubular epithelial cells.[8] In neuropathological diseases, redundant cargoes can have consequences on neighboring cells, such as the scattering of toxic amyloids. Thus, explicitly inhibiting the uptake or biogenesis of these extracellular vesicles could be a potential therapeutic approach.

Extracellular Vesicles in Alzheimer's Disease

Alzheimer's disease is a type of dementia that causes problems with recollection, thought, and expression. Alzheimer's accounts for 60-80% of dementia cases, although the etiology is mostly unknown.[15] Alzheimer's is characterized by the extracellular accumulation of amyloid-β (Aβ peptides) in the brain. The amyloid precursor protein is cleaved by γ-secretases to generate amyloid-β, which can accumulate into plaques causing neurological deficits.11 Although challenging to study, many advancements have been made in the role of extracellular vesicles in Alzheimer's disease.[11,14,15] Mature microRNAs (miRs) are small, endogenous, noncoding RNAs involved in the post-transcriptional regulation of target RNAs.15 Recent research has shown a link between exosomal miRs and the accumulation of amyloid precursor protein leading to the development of neurological deficits.[10]

Liu et al. provided some of the first pioneering evidence suggesting a link between miRs and neurodegenerative diseases.[11] The group identified miR-193b as a potential biomarker for Alzheimer's disease through bioinformatic studies comparing serum and CSF levels between patients and transgenic mice (Fig. 2). The group also found a reduction in amyloid precursor protein mRNA in SH-SY5Y cells overexpressing miR-193b. Furthermore, a miR-193 inhibitor oligonucleotide led to the upregulation of amyloid precursor protein in the same cells. As summarized in Figure 2, they measured the levels of exosomal miR-193b in CSF and serum from wild-type and double-transgenic mice (APP/PS1) carrying mutations in amyloid precursor protein that cause protein aggregation similar to Alzheimer's disease.[11,16] Levels of miR-193b were reduced in both the serum and CSF-like fluid of transgenic mice compared to wild-type mice at 3, 6, and 9 months postnatal. In their patient cohort, exosomal miR-193b decreases in CSF, serum, and plasma of Alzheimer's disease patients,

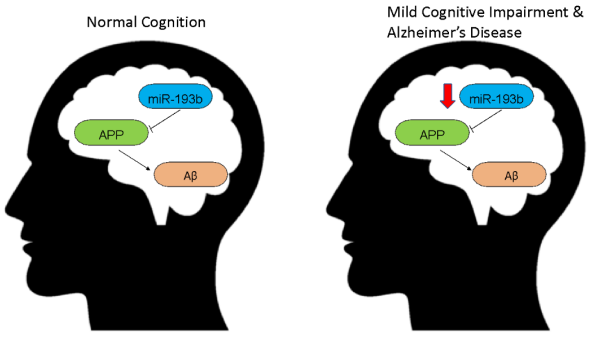

Figure 2. *Role of miR-193b in neurodegenerative diseases. Decreased miR-193b levels are associated with an increase in cognitive impairments associated with Alzheimer's disease. Arrows indicate levels of miR-193b within the cerebrospinal fluid. Reduced inhibition from miR-193b in Alzheimer's disease causes increased amyloid precursor protein (APP) mRNA leading to increased APP, causing amyloid plaque-induced neuronal death.*

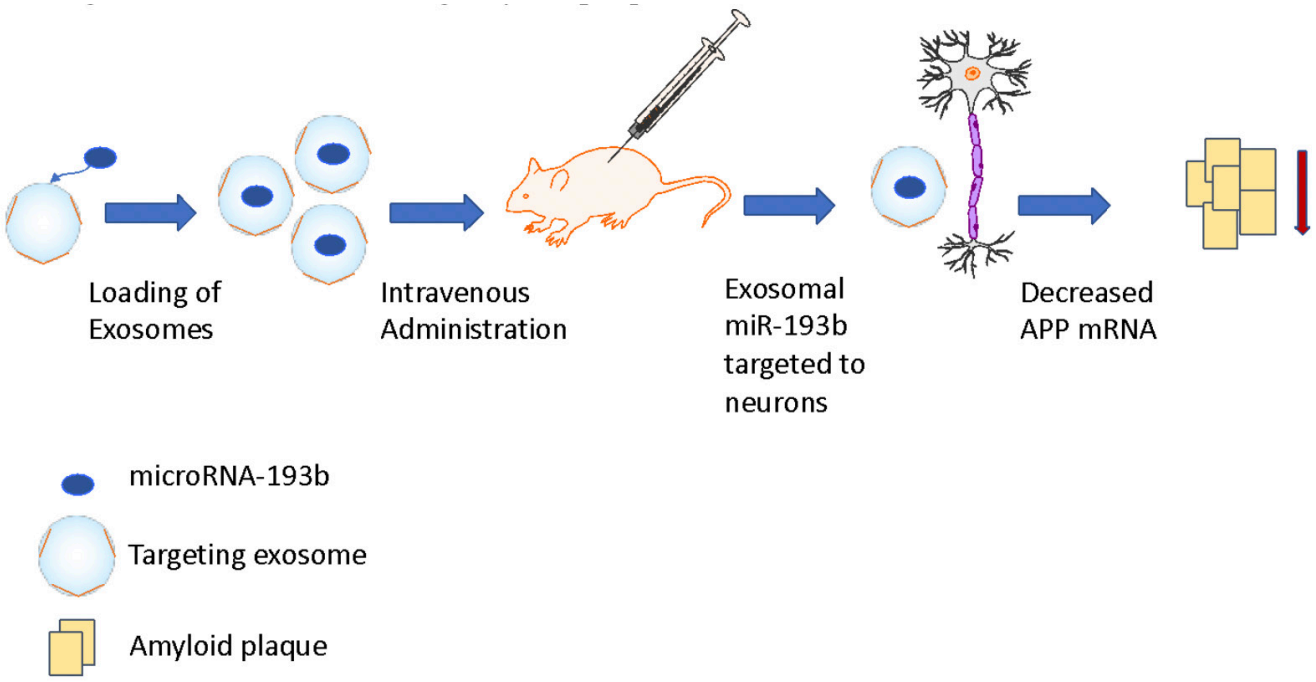

Figure 3. *Hypothetical result of intravenous injection of targeted synthetic exosomal miR-193b. Exosomes are isolated from dendritic cells carrying a targeting plasmid (Lamp2-RVG) and are loaded with miR-193B. Exosomes are intravenously injected into wild-type and APP/PS1 double transgenic mice. Increased exosomal miR-193B in mice brains will reduce amyloid precursor protein and subsequent amyloid plaque formation.*

and to a lesser extent in mild cognitive impairment patients, compared to healthy individuals. As shown in cells, mice, and humans, low levels of exosomal miR-193b may lead to increased amyloid precursor protein, causing the progression of neurodegenerative disorders.[11] Thus, detectable changes in miR levels in CSF may become a vital tool in the early detection of Alzheimer's disease.

Future Directions

The potential benefit of miRs in the diagnosis and treatment of numerous diseases like cancer, infection, and neurodegeneration has been extensively studied. However, few unifying themes are emerging on the requirement, localization, or function of exosomal miR in the many diseases in which they are implicated.[7] Thus, different synthetic exosomal miR therapies must be studied. MiR-based therapeutics have a host of challenges that must be overcome before assessing their efficacy in humans. A significant challenge is ensuring the delivery of the miRs to the right cells in the body. Delivery across the blood-brain barrier is an enormous hurdle for therapies involving brain disorders like Alzheimer's disease. However, Alvarez-Erviti et al. showed that exosomes could deliver siRNA to the brain of mice when injected intravenously.[17]

To further study the effectiveness of exosomal miR-193b as a treatment for Alzheimer's, a similar strategy used in Alvarez-Erviti's work can be applied (Fig. 3). Exosomes can be purified from dendritic cells engineered to express Lamp2b, an exosomal membrane protein, fused to central nervous system-specific rabies viral glycoprotein (RVG) peptide which exclusively binds to the acetylcholine receptor.[15,17] Synthetic miR-193b could be added to the dendritic exosomes using electroporation. Loaded exosomes would then be injected intravenously to age-matched wild-type and APP/PS1 double transgenic mice (used in Liu et al. study). These exosomes containing synthetic miR-193b will be exclusively targeted to neurons, microglia, and oligodendrocytes through the bloodstream.[17] Next, levels of amyloid precursor protein can be quantified by western blot. Memory studies can also be performed to assess the ability of synthetic miR-193b to rescue neurodegenerative phenotypes (Fig. 3). For example, a fear-conditioning experiment could be set-up to test the ability of mice to remember a shock stimulus when paired with a bell. Mice with more severe neurological deficits will have a shorter freeze time when the bell is unpaired from the shock stimulus.[18] Once the cognitive impacts of synthetic exosomal miR-193b are tested in mice, the same strategy could be applied to humans if no adverse immune responses or side effects occurred.

Although the roles of exosomes in cargo transport are essential, and numerous, little is understood of the impact of most exosomal proteins and miRs in Alzheimer's disease.[2,19] The expression profiles of miRs are known to be altered in several regions of brain with Alzheimer's disease, making a robust case for studying how individual miRs contribute to neurodegeneration to determine the efficacy of potential therapeutics.

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Ping Pong: Delivering Bad News Through a Translator

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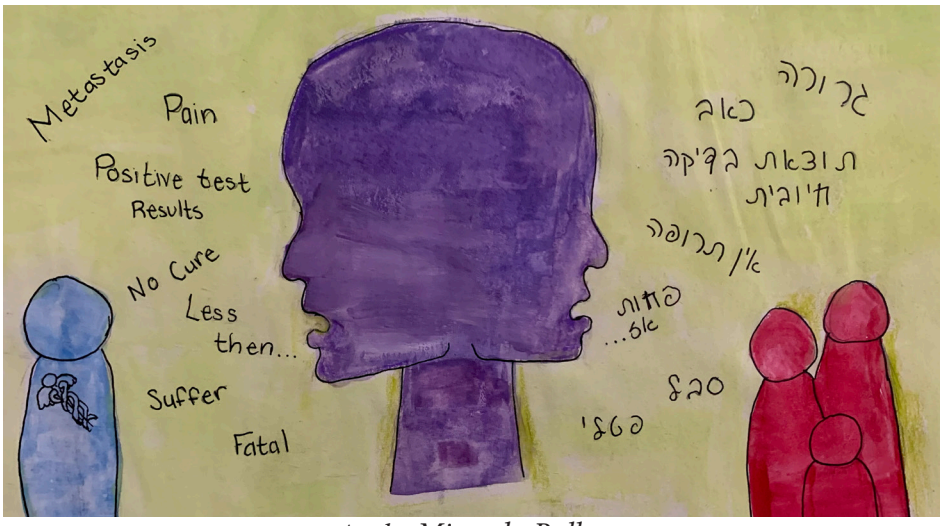

Art by Miranda Roller

I shifted in my seat, folded my hands in my lap, and took a deep breath. The layer of sweat on my upper lip was thankfully hidden by my mask. The parents from Gaza sat across from the pediatric oncologist, cradling their one-year-old son. Words were not needed for these parents to understand that grave news was to come. As the medical student, I sat in the corner behind the physician, a passive observer of the tornado of emotion hurtling our way. Although the connection between the parents and the oncologist was essential, their eyes rarely met. The translator was the center of attention, their eyes darting back and forth, their lips dancing between languages.

The physician began by gauging the parents' understanding of the meeting's purpose. There was a palpable pause as both parents looked toward the translator. The translator repeated the question in Arabic and the parents replied. As the message was relayed, the father began tapping his foot, the mother bounced her baby a little faster on her lap. After what felt like an hour of ping pong, eyes moving back and forth during the translation, the doctor delivered the devastating news that their son may not live past his second birthday. The doctor added that due to the genetic inheritance pattern of this disease, the couples' future children would have a 25% chance of inheriting the same disease and prognosis.

At that moment, the translator's eyes widened. The color left her face and the translator was paralyzed. She understood the gravity of what was about to be said. She knew that the mother was two months pregnant. The parents pleaded for the translator to speak. The intermission in translations, filled with silence and anticipation, heightened the sensations in the room.

The translator took a moment to regain her composure and clarified with the doctor what she would say. The doctor nodded. After receiving the translation, the mother stood up slowly from her chair, her hands shaking as she passed her baby to her husband's lap. She made her way to the window, her empty gaze undoubtedly consumed with the fate of her unborn child.

The palpable silence in the room was enough to signify that the translation was accurate. I never would have imagined that my most impactful lesson in patient-physician communication would be in a foreign language. Only by removing language was it made obvious that the nuances of human connection and conversation are expressed in a language much richer than words.

The moments of silence and anticipation showed me how translation is more than just exchanging words in different languages; it requires the skill of communicating information in a way that is culturally and contextually compassionate.

A Case of Multiple Sclerosis Presenting as Partial Third Nerve Palsy

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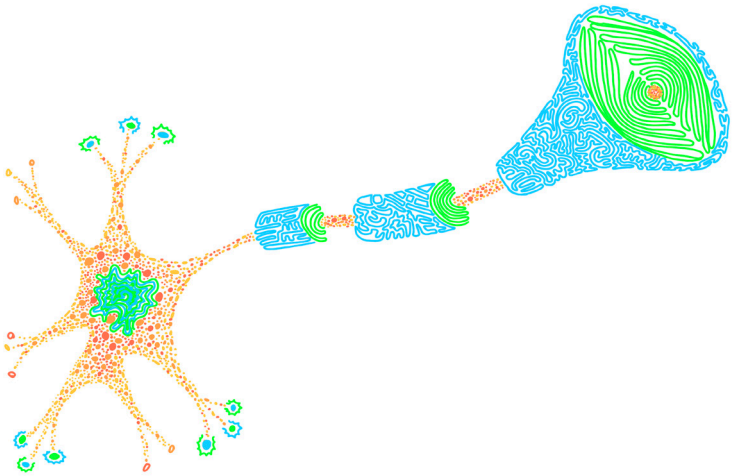

Art by Neena Carr

Abstract

Background: Multiple sclerosis is a demyelinating neurodegenerative disorder with a vastly unknown etiology. The prevalence of pediatric multiple sclerosis is increasing globally. This report presents a case of multiple sclerosis in a 10-year-old patient and discusses preferred methods of diagnosis and treatment.

Case: A 10-year-old previously healthy female presented with sudden-onset left eye pain, diplopia, strabismus, and blurred vision. The clinical evaluation suggested a partial oculomotor nerve palsy. Upon radiographic evaluation, a diagnosis of pediatric multiple sclerosis was suspected. The patient was treated acutely with intravenous pulse steroid therapy and will be evaluated as an outpatient for possible initiation of long-term disease-modifying therapy.

Discussion: This previously healthy patient developed sudden-onset monocular symptoms. Due to the rarity of pediatric multiple sclerosis, other etiologies, such as neoplastic space-occupying lesions, were considered. Radiographic imaging supported a diagnosis of pediatric multiple sclerosis, although, given the first occurrence, a definitive diagnosis could not be made. Following a 5-day course of pulse steroids, ocular symptoms improved significantly.

Contribution to Field: The study of pediatric-onset multiple sclerosis remains largely undiscovered and continues to be explored. This case report will contribute to our knowledge of pediatric multiple sclerosis, and may inform future studies regarding diagnosis, treatment and prognosis.

Case Presentation:

History of Present Illness

The patient is a fully vaccinated and previously healthy 10-year-old female who presented with a one day history of acute onset left eye pain, monocular horizontal diplopia, strabismus, and blurred vision that began upon waking. She describes constant pressure behind the eye, rated 7/10 in severity, which does not change with eye movement and does not radiate. No medications were taken to alleviate the

High Yield Learning Points

- **Multiple Sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system.**
- **MS is more common in females than males, and more common the further one is from the equator.**
- **The most common type of MS is the relapsing-remitting type, which has the best prognosis.**
- **The most common first manifestation of MS is impaired vision due to optic neuritis.**
- **The classic triad (Charcot's neurologic triad) in MS is scanning speech, intention tremor, and nystagmus.**
- **Magnetic resonance imaging (MRI) is the diagnostic test of choice and shows multiple, asymmetric, often periventricular white matter lesions.**
- **Lumbar puncture shows an increase in IgG index, or at least two oligoclonal bands not seen in the serum.**
- **Pediatric MS accounts for about 5% of MS cases.**

Article Ref No.	Year Published	Age	Sex	U/B	C/P Palsy	Pupil involved	Ptosis	Eye Pain	Positive brainstem MRI	Oligoclonal bands +	Isolated to CN III	Initial presentation of MS
4	2018	24	M	U	P	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	2018	40	F	U	P	No	Yes	No	Yes	Yes	Yes	Yes
5	2014	11	F	B	Unk	No	Yes	No	Yes	NP	No	Yes
8	2011	30	M	B	Unk	No	Yes	No	Yes	Yes	No	Yes
9	2011	34	F	B	Unk	Yes	Yes	No	Yes	Yes	Yes	Yes
10	2010	Unk	Unk	Un	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
11	2008	28	M	U	Unk	Unk	Yes	No	Yes	Yes	Yes	Yes
6	2008	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Yes	Unk	Yes	Yes
6	2008	Unk	Unk	Unk	Unk	Unk	Unk	Unk	No	Unk	Yes	Yes
12	2008	35	F	U	P	No	Yes	Yes	No	Unk	Yes	Yes
13	2006	53	F	B	Unk	No	Yes	No	Yes	Yes	No	No
13	2006	37	F	B	Unk	No	Yes	No	Yes	Yes	Yes	No
14	2003	30	F	U	C	Yes	Yes	Yes	No	No	No	Yes
15	2002	36	F	U	Unk	Yes	Unk	Yes	Yes	Unk	Yes	No
16	2000	27	F	U	P	No	No	No	Yes	Yes	Yes	Yes
7	1997	50	F	Unk	Unk	Unk	Unk	Unk	Yes	Unk	Yes	Yes
17	1990	27	M	Unk	P	No	Unk	Unk	Unk	Unk	Yes	Yes
18	1990	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Yes	Yes	Yes	Yes
19	1986	23	F	U	C	Yes	Yes	Yes	NP	NP	Yes	Yes

Table 1: Cases of MS Presenting as Third Nerve Palsies

F=Female, M=Male, Unk=Unknown, U=Unilateral, B=Bilateral, C=Complete, P=Partial, Y=Yes, N=No, NP=Not performed

pain. The patient denies recent trauma, infection, introduction of new medication, or any prior episodes. The patient denies other ophthalmologic symptoms such as conjunctival injection, discharge, or itchiness in or around the affected eye. Upon further review of systems, the patient denies fever, neck stiffness, lethargy, abnormal movements, impaired consciousness, weight loss, night sweats, dizziness, sensory or motor deficits, bowel or bladder function impairments or behavioral changes. The remaining review of systems yielded no appreciable findings.

Family & Social History

The patient comes from an Arabic background with no family history of childhood diseases or autoimmune conditions. The patient is normally healthy with no chronic conditions or medication use. She has no known allergies or sensitivities.

Further Workup

Upon admission, the patient's vital signs were all within normal limits. On the physical exam, the patient was alert and oriented without signs of respiratory distress. Eye examination revealed reactive pupils with proptosis, hypotropia, and exotropia of the left eye. There was limited adduction of the left eye, upbeat nystagmus of the left eye when looking up and to the right, and mild ptosis, more so on the left, which all suggested a partial third nerve palsy. The remainder of the cranial nerve exam was normal. There was normal and symmetric sensory and motor strength seen in the upper and lower limbs, with strong reflexes throughout and no lymph node enlargement. Her labs showed vitamin D deficiency (27.7 ng/dL), and cerebrospinal fluid (CSF) was positive for oligoclonal bands. Otherwise, her lab findings were normal. Head CT/Head-Neck CTA showed no evidence of thrombosis, dissection, or hemorrhage. Brain MRI showed diffuse abnormalities in the white matter consistent with MS.

Differential Diagnosis & Plan

In summary, this 10-year-old patient presented with sudden onset left eye pain, strabismus, monocular horizontal diplopia, and blurred vision that began in the morning. There was no recent trauma, infections, or new medications, no signs of meningitis or encephalitis, and no additional sensory or motor weakness. Examination revealed left eye hypotropia, exotropia, ptosis, limited adduction, and vertical nystagmus. Initial workup revealed vitamin D deficiency, oligoclonal bands in the CSF, and disseminated white matter lesions on MRI.

The differential diagnoses included: demyelinating disease – including pediatric MS and neuromyelitis optica spectrum disorders, both of which often present with acute eye movement abnormalities and disseminated white matter lesions on MRI; neoplasm–glioma or medulloblastoma, supported by the patient's cranial neuropathy, but unlikely due to the acute onset and absence of systemic symptoms; inflammatory condition – Tolosa-Hunt syndrome (THS) or ocular myasthenia gravis (OMG), which were supported by the presence of retro-orbital

Category	Results
Total Cases	19
Age Range	11-53
Sex Distribution	11 F, 4 M, 4 Unk
Unilateral/Bilateral	8 U, 5 B, 6 Unk
Complete/Partial	2 C, 5 P, 12 Unk
Pupil involved	5 Y, 8 N, 6 Unk
Ptosis	11 Y, 1 N, 7 Unk
Eye Pain	5 Y, 8 N, 6 Unk
Positive brainstem MRI	13 Y, 3 N, 2 Unk, 1 NP
Oligoclonal bands +	9 Y, 1 N, 7 Unk, 2 NP
Isolated to CN III	14 Y, 4 N, 1 Unk
Initial presentation of MS	15 Y, 3 N, 1 Unk

Table 2: Summary of Findings in Table 1

U=Unilateral, B=Bilateral, Unk=Unknown, C=Complete, P=Partial, NP=Not performed

pain and cranial nerve (CN) III symptoms (primarily THS), but are extremely rare diagnoses that should be considered when all else has been excluded. Of all possible differential diagnoses, demyelinating disease was most supported by the acute onset of isolated ocular symptoms, vitamin D deficiency, and CSF and MRI findings.

Because a diagnosis of pediatric MS was suspected, the patient was treated empirically with a course of pulse steroids (IV SOLU-Medrol 1000 mg) for three days and reevaluated periodically for clinical improvement. Omeprazole 20 mg P.O. was also prescribed due to the risk of acute gastritis following steroid therapy. Lastly, vitamin D 2000 mg P.O. was prescribed, and the patient was advised to continue vitamin D supplementation following discharge due to deficiency. Following five days of steroid therapy, the patient reported significant remission of symptoms. The patient was discharged and recommended for an outpatient follow-up to discuss initiating long-term disease-modifying therapy.

Conclusion:

Pediatric MS is understudied, underdiagnosed, and less understood than adult-onset MS. While pediatric MS is significantly less prevalent than adult-onset MS, cases such as the one described above illustrate the need for timely identification, diagnosis, and treatment. Data has shown that pediatric MS has a slower disease progression than adult-onset MS. Pediatric patients with MS tend to reach disability younger than adult patients with the condition.[1] Thus, immediate care is even more crucial, as the disease burden is greater earlier in life. Despite the growing number of disease-modifying drugs for MS, there remains no universal standard-of-care, leaving individualized treatment to be determined by each provider. Not only does this result in diverse treatment options, but it also stalls the progression of research, as there is no standardized plan to measure patient outcomes. These disease-modifying drugs, including IFN-B and glatiramer acetate, have significantly decreased inflammation on MRI. Early treatment and strong adherence to therapy are crucial for slowing disease progression and minimizing disease symptom onset.[2] Continued research is crucial to better understand the presentation of patients such as the one described above and to navigate the implications of early diagnosis and treatment vs. a thorough work-up to exclude other pathologies. Most notably, continued research is needed to better understand the course of pediatric MS long-term, and specific areas that are affected in development.[3] Lastly, as the patients are young children and adolescents, more targeted strategies to improve patient compliance are critical to improving patient care.[3] As more patients present with similar symptoms, it is crucial to contribute each patient's presentation, treatment, and disease course to the growing database of similar patients. This will aid ongoing research worldwide to improve outcomes and quality of life for those with early-onset MS.

Literature Review:

The existing literature is scarce in reports specifically about third nerve involvement in multiple sclerosis. According to Scelfo et al.,[4] "the rarity of CN symptoms is thought to be a function of the relative lack of myelination surrounding the CN nuclei compared with extensive myelination seen in other portions of the brainstem such as the medial longitudinal fasciculus." This may explain why manifestations of MS such as internuclear ophthalmoplegia (INO) and nystagmus are seen much more commonly. A search of the literature only produced a single case of third nerve palsy reported in the pediatric population. In 2014, Adam et al.[5] reported on the case of an 11-year-old female with no previous medical history who presented

with bilateral oculomotor nerve palsies without pupillary involvement and bilateral optic neuropathy. Her history revealed that she also had intermittent hypogeusia and emotional lability two weeks before the onset of her visual symptoms. Contrast-enhanced brain MRI showed hyperintensities scattered throughout the white matter, including the basal ganglia, frontal periventricular area, and midbrain. Myelin basic protein and oligoclonal band testing were not performed due to an insufficient CSF sample volume. Initially, a working diagnosis of acute disseminated encephalomyelitis (ADEM) was made, while pediatric MS was considered. MS was confirmed on her second presentation 6 months later when she was admitted for confusion, ataxia, and dysarthria.[5] To the best of our knowledge, our case represents the first report of pediatric MS presenting as monocular partial third nerve palsy.

There is more literature about third nerve involvement in adult MS; however the condition has proven to be quite rare. According to a retrospective analysis performed in 2008 by Zadro et al.,6 data from 483 CIS (clinically-isolated syndrome) and MS patients demonstrated isolated cranial nerve involvement in only 10.4% of patients. Moreover, third nerve palsy was found in only 2 (0.4%) of the patients, and the palsy was the first presentation of MS for both patients. In a study performed in 1997, Thomke et al.[7] found isolated cranial nerve palsies in 1.6% of MS patients. Zadro et al. attributes the difference (10.4% vs. 1.6%) in findings to their study, taking into account isolated cranial nerve V palsies that were not included in the earlier study. These studies found that isolated cranial nerve palsies more often occur as initial presenting symptoms rather than during disease relapse.

Table 1 below data from all case reports specifically discussing third nerve palsies as manifestations of MS. Only 19 cases of MS presenting with third nerve palsy were described in the literature. The youngest patient was 11 years old, while the oldest was 53 years old. There were 11 females, four males, and four unidentified patients. Nine presented with bilateral third nerve palsy, four presented with unilateral third nerve palsy, and six were not specified. Thirteen patients had a positive brainstem MRI, three did not, one was unknown and one did not perform an MRI. Nine patients had positive oligoclonal bands, one did not, seven were unknown, and two did not perform the exam. Fourteen patients had isolated third nerve palsy, while four did not, and one was unknown. Fifteen patients' initial presentation of MS was third nerve palsy, and for three patients, it occurred during a subsequent episode of MS. The status of one patient was unknown.

Given that third nerve palsy is a rare manifestation of MS, particularly as a presenting symptom, this case report was written to increase awareness of this presentation. The goal is to lead physicians to consider MS in their differential diagnoses to avoid delaying valuable treatment.

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Reproductive Technology and its Relationship to Halakha

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Art by Talia Ditkoff

Young Jews all over the world are told that Judaism is a dying religion, and therefore it is their responsibility to marry other Jews and conceive Jewish babies to carry on the religion and pass on traditional customs. This principle pervades both cultural expectations and religious doctrine, as one of the 613 commandments of the Torah is to be fruitful and multiply. Creating a Jewish family is quite literally a religious expectation.

As reproductive technologies become commonplace, one would assume that this goal would be more easily achieved, even for couples who face fertility issues. However, Jewish ritual law is very strict about what procedures can be done to the body, and what constitutes a Jewish family. So, where does that leave religious Jewish couples who cannot safely have children on their own? A Torah Infertility Medium of Exchange (A TIME) is an organization which aims to provide support and resources for Jewish couples with fertility struggles. By exploring the organization's contents, one can gain a better understanding of the complex relationship between Jewish religious law (halakha) and science as it pertains to reproductive technology. It is important for us, as future medical providers, to learn how we may assist religious couples struggling with infertility to receive appropriate medical care that is congruent with their religious values.

There are a wealth of differing opinions on this topic because Judaism is an ancient religion. Rabbinic figures must constantly evaluate the new reproductive technologies to ensure that they remain within the bounds of halakha. To do so, rabbis have had to extrapolate meaning from ancient texts and apply fundamental Jewish principles to modern times.[3] Since rabbinic rulings on reproductive technologies are based on texts that do not directly address the contemporary advancements of reproductive science, there is great room for interpretation.

The existence of websites such as A TIME emphasizes the potential compatibility between reproductive technology and halakha, or at least the possibility for overlap between the two, given that the website's goal is to provide fertility resources for religious Jewish couples. The website's services and support systems cover a wide range of perspectives, which emphasize the integration between science and religion that is required for a religious couple to conceive using reproductive technology.[1]

This website provides a starting point with whichto further explore the complex relationship between reproductive technology and halakha. The first major question is whether infertility treatments such as in vitro fertilization (IVF) are able to be compatible with Jewish religious law. As previous-

ly mentioned, one of the 613 commandments of the Torah is to be fruitful and multiply. However, there are also rules explicitly against the cutting of sperm ducts and wasting seed (i.e. masturbating), both of which would be required in order to conceive a child through IVF. Consequently, rabbinic authorities must decide which commandment takes precedence. Most rabbis have ruled that procreation should be prioritized, even if it requires collecting sperm in an undesirable fashion.[3] If we accept the rabbinical resolution that IVF is indeed permissible in Jewish law, other practical questions arise.

The next question pertains to gamete donation since fertility issues are often the result of unhealthy or nonoptimal gametes, whether it be sperm, eggs, or both. Most religious rabbinic authorities have concluded that gamete donation breaks the sacred bond between a husband and his wife, equivalent to infidelity.[3] That being said, if we assume that gamete donation is permissible, there are many complications to consider. Since Judaism is traditionally passed down through the maternal line, use of a sperm donor should not influence the religious identity of the child conceived. However, the issues surrounding donation of maternal genetic material or womb space become exponentially more complicated. Is it the genetic material or the origin of the womb that provides a child with their Jewish status? If the former is the case, a child conceived from an unknown egg donor, but carried to term and delivered by a Jewish woman would not be considered Jewish. However, a child conceived using the egg of a Jewish woman, but carried to term and delivered by a non-Jewish surrogate would be considered Jewish. This uncertainty has left many new parents without a halakhic consensus, often resulting in the parents opting to convert the child to Judaism as a precautionary measure. Recent thought has revealed a rabbinical leaning towards the latter, in that the Jewish identity of the child is dependent on the womb of the woman rather than the genetic material. This is seen in the rabbinic approval of ovary tissue donation in contrast to the prohibition against egg donation.[3] More support for this approach is found in the widely accepted belief that the soul of the child is not established until about six weeks into the pregnancy.[3]

Revisiting the concept of wasting seed opens the door to more questions regarding kosher reproduction. After embryos are prepared for implantation, leftover embryos and genetic material always remain, as women are not capable of safely carrying all of the embryos produced. However, rabbinic authorities hold that if the intention is to be fruitful and multiply, this procedure is permissible.[3] This concept is extended to approve the use of leftover genetic material for life saving research or helping other Jewish couples to conceive.[2]

What kind of assisted reproductive procedures requires rabbinic supervision? This question does not seem to have one clear answer. It is well accepted that supervision is necessary to ensure that no other sperm or egg were used aside from that of the couple.[3] However, it is unclear as to what other aspects of IVF require supervision. It could be assumed that the disposal, or lack thereof, of leftover genetic material is probably supervised, but the uncertainty of the process as it pertains to Jewish ritual and law leaves much to be explored.

As we move into a time where genetic knowledge is increasing and reproductive technology is advancing, more questions will continue to arise. For example, determining maternal parentage for a child conceived using three-parent technology, created by the sperm of one man, the nucleic DNA of one woman, and the mitochondrial DNA of a second woman, will be a complicated matter with no halakhic precedent. Similarly, when the time comes that a child may develop in an artificial womb, the question of matrilineal descent will arise again, since it has already been established that the womb in which the child develops is more important than the genetic material of the child when determining the Jewish status of a child.

Overall, it should be noted how complex this topic is and just how many Jewish couples around the world are impacted by these issues. Among the religious Jewish community, the societal pressure to immediately conceive after marriage looms over the heads of young Jewish couples. As such, there is a massive stigma associated with fertility difficulties, and because reproductive technology is relatively new, there are many disagreements regarding whether and how medical interventions to conceive a Jewish child are compatible with halakha. As a result, infer-

tility struggles cause many members of the Jewish community to feel alienated in their struggle to start a family naturally and by the perceived dissonance between their religion and newly available methods of conception. As our society progresses and reproductive technology becomes more accessible to the public, hopefully rabbinic approval of new reproductive approaches will continue to increase. We as medical professionals will be able to lead the way in allowing Jewish couples with fertility difficulties to feel more accepted.

Medical care can be made more accessible to minority groups through our understanding of these cultural intricacies. By better understanding these nuances, we may provide both physical and spiritual care. In places like Israel, these nuances are regularly taken into consideration within the healthcare system due to the religious influence in the governance of the country. As future healthcare providers in the United States, we too must take into account the personal aspects of a patient's life to provide them with holistic care for their physical ailments in a way that aligns with their religious beliefs.

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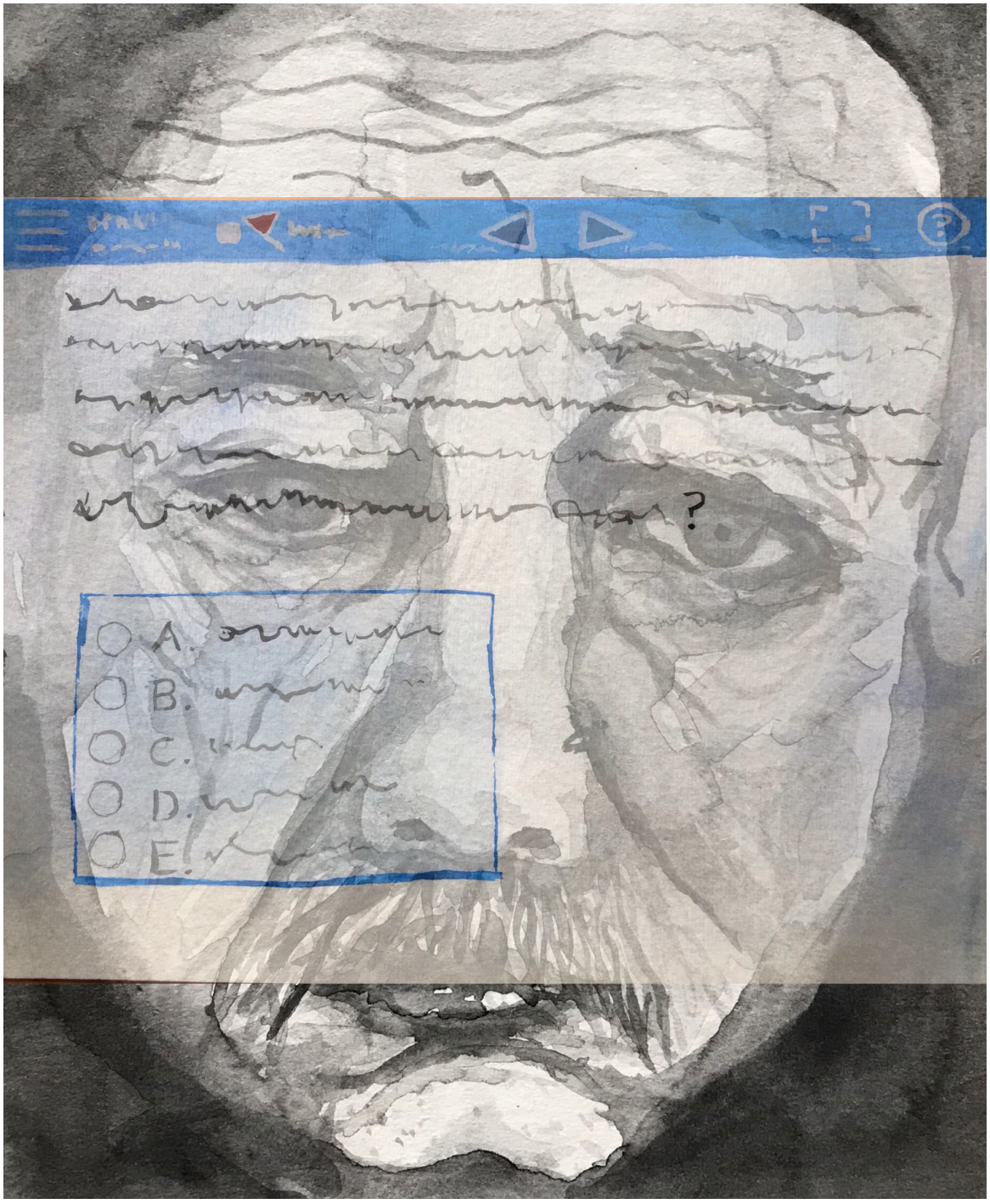
Sackler Art of Medicine Spring 2022 Contest Winners



Art by Lital Avni-Singer

Untitled

By Dania Halperin

"A 72 year old woman is brought to the emergency room…… has not been able to eat and drink in 2 days…..serum glucose 72mg/dl…..urine ketones….. right hip fracture….answer is Hormone sensitive lipase, next."

When reading a clinical vignette, we are taught to always read the last line or two first - it's usually the most important part. This is probably some of the best advice I got for solving U-World questions. The vignettes are long, and you usually have to just skim most of it and keep your eyes sharp for the 1-3 words or phrases that are key to the answer.

My 79-year-old grandfather called me a few weeks ago and told me it doesn't hurt when I pee but sometimes it looks like there may be some blood. But don't worry it doesn't hurt and it's probably just another kidney stone or something.

Translation: A 79-year-old man presents with a 3-month history of painless hematuria with a remote history of kidney stones. My mind jumps to page 629 in First Aid: bladder cancer. I'm taking my NBME for Renal/ Hem/ GI this week, I know this information. I don't say anything - I tell him to go see a doctor, and he makes an appointment.

"A 72-year-old woman is brought to the emergency room after lying on the floor for the past two days."

My grandfather sees the doctor who refers him for scans. Turns out there is a bladder mass, and they need to biopsy but it's definitely cancer. They will remove it and it will be ok.

"The patient's neighbor called the police after phone calls were not answered and no one opened the door"

My grandfather undergoes a procedure to remove the cancer and the biopsies are sent to pathology to figure out the diagnosis and to see if the cancer has spread. They remove a large mass.

"She is found awake on the bathroom floor lying in feces and urine."

The pathology report comes back:

Histology – urothelial carcinoma with squamous differentiation…. high grade…..invades lamina propria…. invades muscularis propria. Diagnosis is transitional cell carcinoma grade 3. Part of me pleasantly surprised how the words are no longer foreign but I'm shocked because I wasn't wrong, but this isn't another U-World question. I can't skim this one because its real. But aren't they all real?

"The patient says she fell and injured her right hip and was unable to get up to call for help. She did not drink or eat anything in that time."

This poor woman - imaginary yet no less real than my grandfather – fell and fractured her hip and was lying alone on her cold kitchen floor for 2 whole days because no one was there to help.

I've gone back to that question a lot lately – not to the final line, but to the deeply human, desperate, and lonely vignette that I have been taught to skim over. This is something that happened to someone; all these cases are real, and they happen to real people. We all know it, but for now we need to skim and focus on the answer. The actual story isn't the "high yield" part in medical school – we focus on the educational objective listed below the practice question:

"Educational objective – Hormone sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates for hepatize gluconeogenesis and ketone body formation."

My grandfather is the strongest person I know, and he's optimistic so we will be optimistic with him. The doctors have taken their NBMEs and STEP exams and are trained to know what to do. I will get there at some point too and so will the rest of my class. These are our future patients.

We are learning to understand disease through these questions, but we must also learn to understand the people in them. Until then, I have some U-World questions to do.

- In honor of my Opa, who I love very much.

Icarus

By Ethan Feig

I saw my first God a month before my father died. I remember his office, tucked away in the quiet recesses of the hospital, with an open door for my mother and me. My father was already inside, what was left of his emaciated frame barely leaving an indent on the cushioned seat.

I sat on my mother's lap as he spoke to us. I remember her reverence, the way that my father's sunken eyes swallowed every word. The God told us that despite our faith, despite our devotion, my father would die of cancer. Everything he said had come true, and this was no different. Life was something he could foresee and foreclose.

It was after he died that I started pulling ahead in school. No matter whether we had a place to live or food to eat, I refused to miss a single day. When I graduated high school a year early with a full-ride to an Ivy-league university, my mother said it was the happiest day of her life. I was happy too, but I wasn't surprised. It was easy for me. I knew how intelligent I was, and so did the kids that picked on me at school. The only time I tried at anything was my medical school interviews. I had the grades, the MCAT scores, and more physician shadowing than I could fit on my CV. But even then, the interview scared me. For a whole day, I had to sell a lie to the admissions departments, sell them on believing that I was really in it for the 'right' reasons. For helping people, for the passion of it, for giving people the 'gift of life.' I wanted to become my own God, to show everyone else how it should be done.

Once I got in, the rest was easy. I collected knowledge and devotees without bothering to make a single friend. I knew very early on that I was going to be a surgeon. I knew I was qualified to control life at my fingertips. My patients would pray for salvation by my hand. I imagined they would recognize me years later at an exclusive bar with a beautiful woman on my arm and pay for our drinks out of gratitude. My residency went smoothly, especially since I was more capable than any of the other surgeons after six months. I was untouchable.

After two tedious years, I was finally a full-fledged cardiovascular surgeon. I did the general surgeries that anyone with a brain could handle for a year, then got the chance to move onto the interesting stuff. Coronary revascularizations, septal myectomies, and aortic dissection repairs kept me busy for the next ten years. I specialized in the kinds of surgeries that made the rest of them shake their heads and say it couldn't be done. I had patients fly in from all over the world, spend more money than they made in a year, just for a few hours under my scalpel.

It was mid-December when it happened. Another surgeon in the department had to go to his grandmother's funeral, or had a wedding or something like that, so I took his work for the day. He apparently had already told the patients that I would be doing his procedures instead. I'm sure they looked at my record and didn't mind the free upgrade, so I didn't bother to meet them. The first guy was a triple bypass, easy enough. By the time I walked into the OR, the patient was already prepped. Time-in. As soon as I was handed my scalpel, I removed the blue drapes around his leg and made my first incision. The wet slurp of suctioned blood cleared the way for me to advance past the muscle tissue and into the venous space. The help was slow, but it didn't matter. I inserted my hand into the incision, moving past the curdled-yellow fat cells. My fingertips disappeared into the red soup, slowly descending to my knuckles. I could feel the femoral artery pulsing directly beneath my middle finger and used it as a landmark to find the nearby veins and isolate them for excision. I knew how long the veins needed to be, and once I had it measured, it was just a matter of cutting and sewing. Once the three veins were all nicely removed and lined up on my stainless-steel tray, the real work began. There's nothing like using a pulsing bone saw to cleave someone's chest open, it really wakes you up in the mornings. It wasn't long before I was laying eyes on the patient's beating heart. It took the technicians a few minutes, but under my observation, the heart-lung machine began to do its work, and the heart slowly twitched to a halt. Now it was time for some finesse. Using threads thinner than a human hair, and cuts smaller than the naked eye could detect, my fingers weaved in and out of the great arteries and vessels, re-routing the blood flow around the blockages that I had seen on the MRI earlier that day. As soon as I was done, I left the room and let my acolytes restart the heart and replace the ribcage.

A quick hand-washing and re-gowning later, and I

was ready for the second surgery, a valve replacement. The only real difference with this one was that I would be going inside the heart, replacing the aortic valve with a synthetic semilunar that had been customized for the patient. The surgery should take an hour and a half, maybe faster, depending on how much my staff impeded me. I parted the ribs of the red sea and made my first incision. I assessed the area supporting the old valve in case I needed to account for it when I placed the new one. Everything seemed normal. I looked at the valve itself, gently flapping its fleshy wings with my finger to spot any tears or gaps. Nothing. The demigod beside me looked over my shoulder, his forehead crinkling under his face shield. He held out a hand to stop me briefly, turned away from the table.

"We're doing the aortic valve, correct?"

The flustered nurse consulted the surgical schedule, but I knew I was correct. I didn't make mistakes.

"Yes, it's the aortic valve."

It didn't matter. It wasn't a physical defect that I could see, and there wasn't anything specific in the pre-op report. I carried on, using my perfect mental maps as a reference to make my incisions. It wasn't until five minutes later that I spotted the same nurse approaching the patient, breaking the sterile field.

"Hey! What are you doing?"

I saw the blood rush from her face. She continued over to the patient's side, exposing his right arm from underneath the blue curtain.

"What the hell are you doing?"

She looked up from his wrist, the laminated hospital band reflecting the bright lights. Her pupils were dilated.

"Sir… this is the wrong patient."

"What?

"There's be – there's been a mistake."

"A mistake?"

"Sir… He's the triple bypass, sir."

I paused.

"You're telling me that I just removed this man's heart valve for no reason?"

It felt as though I had gone out on a walk and somehow fell off the side of the earth. It wasn't something that was possible, until your stomach was already in your throat.

Since I had already discarded the original valve, I had to finish the replacement. It wasn't a perfect fit, but I made it work. Then I had to do the bypass. By the time I was done, I was soaked in sweat and blood. I didn't even get to change out of my scrubs before being cornered by the chief. The first patient's leaky valve blew out due to the extra blood flow, sending him into irreversible cardiac arrest. He never made it out of post-op care.

I had no way of knowing. The patient's names were Taylor Johns and John Tayler, and hospital staff had never been consistent about reading names a specific way. It was also during the holidays, so the staff that might have caught it were already on vacation. They couldn't fire me, but what they ended up doing was far worse. They started supervising me, questioning me, trying to flay me open under my own lights. I was forced to explain every incision, every suture, to these people who knew nothing of perfection.

Of course, both the living and the dead immediately sued me. Although I had malpractice insurance, I soon realized that it wouldn't help much, especially since I had bought the cheapest package. The hospital didn't find any reason to press charges after conducting an internal investigation, but the court needed a villain. I was free in the eyes of the law but condemned by their glint of superiority. They wanted to cut me out like a cyst, now that sadistic lies of my incompetence had driven my patients away, the only ones who were keeping the hospital afloat. They didn't deserve me anymore. I sold the house closest to the hospital and moved into my vacation home down south. I interviewed a few hospitals, but they tried to make me prove my worth. As far as I'm concerned, my record is still spotless. Soon there was nothing to do besides hookers, beaches, and bars.

I can't stop thinking about this perfect storm. I bet someone messed with the schedule on purpose, maybe Ted found out I was banging his wife? Besides, the hospital should have treated me like a hero. I'm probably the only surgeon in the country who could have saved that second patient.

I've conned my way into seeing some pill-peddling psychiatrist, the only way I could get my hands on the heavy-duty sleeping pills. All I had to do was blab about my 'feelings,' choke up about how I've been having trouble sleeping since the hospital screwed me over. I had her wrapped around my little finger after the second session. One more sob story about how my self image was crumbling and she did whatever I wanted. I said I was going out of town to see my imaginary sister so I could get a double dose. You know that feeling when you've just woken up in the morning, and for a split second you forget

everything, even your name or where you are? I think I'll get drunk tonight, take a handful of those pills, and enjoy a well-deserved rest. I'll be fine. I don't make mistakes.

Author's Note

First and foremost, this story is a complete work of fiction. It is not intended to portray any individual, and I'm sure there are plenty of medical inaccuracies that I'll hopefully be able to correct someday.

While learning in classrooms and spending countless hours in the library has earned me a wealth of knowledge, I often take time to remind myself that there is more to this profession. I hope to become a good physician because of my capacity to empathize, not my ability to memorize facts. While writing this submission, I came up with a catchy slogan that I felt summarized things well: health is only half of healthcare. This story was written to showcase the downfall of ignoring these components, of training physicians who are brilliant, but are solely interested in the profession for themselves. I hope to heal with both an open mind and an open heart.

The Line

By Nica Shkolnik

We've all dreamt about it,

Danced around it,

Even paid a fortune for it.

In the hopes of one day

Reaching out and grabbing it.

We've sensed its aura,

Admired it on other people,

And even grew up around it.

Yet the thing itself we do not have.

It will take years, they say.

Four years

Three years

Two years

One more.

Then, you may have it.

The intangibles are the sweetest things. A mirage in the distance,

That sharpens when someone says "ok, you've waited long enough."

It gives validation, a sense of accomplishment.

But the glory is not why we wait.

Arguably, we do not wait at all.

We do not turn our heads to the possibility of adding one or two more years.

Because we know how much we live while we "wait" our turn.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