The promise of personalized medicine: A business–focused perspective

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In 1997, Harvard Business Professor Clayton Christensen published the book, The Innovator's Dilemma, a landmark publication that coined the term "disruptive innovation."[1] The book crystallized a new entrepreneurial approach that, many credit, led to the internet revolution and the rise of the tech giants that dominate the technology–driven world today. The essence of disruptive business theory is that large incumbent businesses are often outcompeted and replaced by competitors with product offerings that are so cheap, and of such low apparent usefulness and quality, that initially they aren't considered threats by the companies that are eventually destroyed.[2] Examples of disruption abound: currently, many areas of manufacturing are poised to be disrupted by 3–D printer technology.[3] Initially considered useless toys, 3–D printers are now being used to print stem cell–derived biological tissue and reusable superalloy rocket motors. Christensen's insights gained him exalted status within the tech sector and millions of entrepreneur disciples.

In 2009, after a series of battles with chronic and acute illness, Christensen published a second book, The Innovator's Prescription, describing the medical industry as a complex interconnected web of third–party health insurers, medical professionals, and regulatory bodies.[4] The author recast the practice of medicine as three interconnected businesses, separating diagnosis, treatment, and communication into a "Solution Shop", "Process Business", and "Managed Network", respectively.

The solution shop: This "business" comprises the diagnostic activity of healthcare workers. Once a problem is diagnosed, a doctor can prescribe a course of treatment to cure the patient. Because the doctor cannot control external and unknown risk factors, the uncertainty associated with this activity generally necessitates a fee–for–service pricing model.

The process business: After diagnosis, a course of treatment can begin. In this business model a "material" is taken in and undergoes a well–studied process that adds value to it. In this case, a patient is treated and cured of disease or ailment. Generally, process businesses operate on a pay–for–outcome model, but this is not the case for healthcare.

The managed network: This part of the healthcare business facilitates communication between experts, and also to patients suffering from chronic diseases, spreading state–of–the–art information about medical practices to interested parties. This type of business usually operates by a fee–for–membership model.

The deconvoluted business model accentuates how each segment of the healthcare market informs and guides the other by a circular feedback mechanism. Currently, doctors are primarily responsible for diagnosis and treatment and the two are often blended together in an iterative cycle until the problem is solved. It is apparent that optimized diagnosis and networking practices would lead to more efficient treatment delivery, and that small diagnostic improvements could have magnified effects in terms of efficient expenditures and the pricing of care. The high value of improved diagnosis and networking, because of its magnified effect on the cost of treatment, makes it an attractive target for disruptive innovation.

The future of medicine in a personalized world

It is obvious to an astute reader that personalized or precision medicine is primarily, in the parlance of Christensen's theory, an improvement to the Managed Network and Solution Shop diagnostic business models. Legions of entrepreneurs and investors are eager to implement disruptive personalized diagnostic technologies that they envision will allow doctors to track the health of individual patients accurately enough to eventually implement a fee–for–outcome model on the process, or treatment side, of the tripartite medical system. Though this dubious future is at best a long way off, personalized approaches to medicine are progressing towards improved diagnostic success along three main trajectories: bioinformatics, personalized diagnostics, and big data analytics. These three broad areas, and how they are poised to change the way we diagnose disease, are described below for the interested reader.

Bioinformatics

Bioinformatics is the study of molecular biology using modern computational methods. In medicine, these technologies are being applied to large data sets of human genome sequences in an effort to extract meaningful links between a patient's health and their genetic makeup. This powerful technique promises, in the near term, to have significant impact in the area of pharmacogenetics, early disease diagnosis and treatment, and personalized chemotherapy, among others.[5]

Personalized diagnostics

Fully implementing a personalized approach depends on the collection of mass amounts of data in order to understand an individual's specific healthcare needs in a meaningful way. Two main avenues of progress are being vigorously investigated. The first is the comprehensive evaluation of individuals through a suite of diagnostic tests to measure genetic and other biomarker data across thousands to millions of variables. These data can inform bioinformatic models and be cross–referenced to existing databases to evaluate a patient's health against the current body of published medical knowledge. The second disruptive personalized diagnostic approach is the use of extremely inexpensive point–of–care, or patient–operated diagnostic devices to persistently monitor health metrics over time.[6] A well–known example of this type of device is the home electrocardiogram machine.[7]

Big Data Analytics

Distinct from bioinformatics is a second computer–aided diagnostic analysis with a much larger scope: big data analytics.[8] This personalized approach expands the breadth of information used to diagnose disease to include all available data. Big data personalization will correlate

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everyday data on a patient's purchases, movement, heart rate, sleep schedule, social media activity, and other metrics with medical data gathered through traditional bioinformatics. In this scheme, low–quality data can be used to accurately track individual and population–level health and inform genetic and biomarker diagnostic data sets.

The power of change—getting involved

Changing population demographics, as Canadians age, guarantees that fundamental changes are coming to the medical system in this country. Personalized approaches are an attractive avenue towards maintaining a sustainable healthcare system. The pace of progress in the quest for effective, widely available, personalized medicine depends on the participation of medical professionals from all segments of the industry—and doctors in particular. Rather than threatening the existing system, these disruptive changes can help preserve healthcare in the face of spiraling, unsustainable cost increases.[9]

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The emerging role of the microbiome in precision medicine: An overview

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Abstract

The advent of precision medicine has promoted an influx of research relating to the identification of patient–specific factors, both genetic and acquired, which could be targeted and manipulated in the context of disease. The microbiome is a particularly good example of a potential target of these measures, as it represents a diverse array of unique, modifiable factors, known to play an important role in both normal human physiology and the development of pathology. Given this, the contribution of the microbiome to human disease, as well as the potential utilization of microbial modulation in prevention and treatment, is a burgeoning area of study. In this review, we summarize the recently established correlations between intestinal microbial dysbiosis and disease pathogenesis in the fields of cardiology, oncology, psychiatry, and immunology, highlighting the specific organisms that have been identified as potential therapeutic targets. However, the practicality and potential harms involved in screening for dysbiosis and manipulating the microbiome need to be carefully assessed before these findings can truly be applied to the world of personalized medicine.

Introduction

The role of the microbiome in human health has been one of the most rapidly evolving fields of medical research in the past several decades. With commensal bacteria making up a staggering 57% of our total body cell count by recent estimates, the microbiome is increasingly being recognized as a distinct organ.[1] The impact of commensal flora, ranging from the widely studied intestinal microbiota to the organisms lining the respiratory and genitourinary tracts, has been studied across many fields of medicine. These microorganisms have been found to have an incredible number of interactions with every body system, from neuroendocrine effects on the central nervous system to the stimulation and modulation of our immune systems.[2] The more we understand about the interaction of the microbiome and its host environment, the clearer it becomes that these microorganisms play an integral role in the development and maintenance of normal physiological functions.

Given our emerging understanding of the importance of these interactions to the healthy functioning of the human body, there inevitably comes the question of the role of the microbiome in disease. Can the interplay between the host and microbiome have an adverse impact on overall health? Where does one draw the line between "healthy" gut flora interactions and pathogenic behaviour? What role does microbial dysbiosis, or the imbalance of microbial composition in favour of more harmful organisms, play in disease pathogenesis?

The remainder of this review will serve as an update on the progress of our understanding of the role of the intestinal microbiome, the most thoroughly researched portion of our commensal flora, in various diseases. While the gut microbiome has been found to play a role in nearly every field of medicine, we will specifically focus on its involvement in the fields of cardiology, immunology, oncology, and psychiatry, as well as the evidence surrounding the correlation between specific bacteria and the initiation and progression of illness. Finally, we will consider the potential for microbial manipulation—whether one day, the knowledge of a patient's specific microbial balance may play a role in the prevention and treatment of disease.

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Role of microbiota in various fields of medicine

Cardiology

The role of the intestinal microbiota in cardiovascular disease has been a point of great interest in recent years. These studies have investigated variances in microbial composition in patients with cardiac risk factors (including obesity, diabetes, hypertension, and dyslipidemia) and have also utilized animal models to determine to what extent the manipulation of flora could modulate the course of their diseases. One study found that the bacterial phyla Bacteroidetes (including Bacteroides and Prevotella) and Firmicutes were disproportionately represented in the flora of obese subjects (both mice and humans), proposing a mechanism by which these specific bacteria were capable of increased energy harvesting from the diet. Even more strikingly, they found that over time, gut–sterilized mice transplanted with a sample of the flora from obese individuals developed significantly more body fat than their lean–transplanted counterparts.[3]

Similar findings were established in the context of hypertension. Hypertensive patients were found to have significant overgrowth of Prevotella and Klebsiella species; furthermore, transplantation of the hypertension–associated microbiota into germ–free mice was also found to significantly raise blood pressure, demonstrating a more causal role for these microorganisms in the pathophysiology of the disease.[4] There have been several studies aiming to characterize the precise mechanism by which these specific bacteria impact metabolism, implicating a set of pro–inflammatory metabolic functions that may contribute to atherogenesis. On the other hand, there is also evidence that the fat–metabolizing properties of certain phyla (particularly studied with Lactobacillus–containing probiotics) may actually provide an atheroprotective effect.[5] Thus, in further understanding the role of different bacteria in the pathogenesis of (and protection from) atherogenesis, we may develop strategies to specifically modulate each patient's microbiome for both the prevention and treatment of cardiovascular disease.

Psychiatry

There has been a great deal of interest surrounding the potential role of the microbiome in the pathogenesis of psychiatric conditions. There have been many studies demonstrating the physiologic

connection between the microbiome and the mind through the relationship between the enteric and central nervous systems. It has been hypothesized that psychiatric pathology could be fueled by neuroendocrine dysregulation secondary to bacterial production of neurotransmitters. The pioneering studies in this field aimed to characterize the difference in microbial composition between healthy subjects and those with mental illness. These studies illuminated several Lactobacillus and Bifidobacterium species, often depleted in patients with depression and anxiety, as key players in the body's stress response via the modulation of the hypothalamic–pituitary axis (HPA) through the vagus nerve.[6] A more direct link demonstrating the effect of microbial dysbiosis on mental illness was demonstrated in a murine model. Transplanting the microbiome from depressed human patients into rats was found to induce significant behavioural changes, including an increase in depressive symptoms (as measured by the sucrose preference test, in which a decreased level of voluntary sucrose ingestion is interpreted as anhedonia) as well as anxiety–like behaviours (measured through validated experimental methods to gauge anxiety in rats, such as the elevated plus maze and the forced swim test).[7] These results raised the interesting possibility that the altered microbiome itself may be a direct player in the pathogenesis of psychiatric disease, as opposed to simply reflecting a by–product of the disease state itself.

In an attempt to apply these findings to the clinical world, there have been several recent studies demonstrating the positive effect of microbial modulation on mental health. Probiotics containing the key contributory bacteria Lactobacillus rhamnosus (often depleted in anxiety and depression) were initially tested in murine models and were found to decrease anxiety/depressive behaviours, likely by inducing changes in GABA receptor expression in the hippocampus and prefrontal cortex.[8] Follow-up human trials with a probiotic containing a separate Lactobacillus strain (L. casei strain Shirota) demonstrated a decrease in salivary cortisol as well as the physical manifestations of anxiety in academically stressed medical students, and another study demonstrated that a mixed Lactobacillus/Bifidobacterium probiotic cocktail was able to decrease cognitive reactivity (including rumination and aggression) to sad mood in healthy subjects, suggesting a possible role for probiotics in the prevention of depression in its early stages.[9-10] However, the human trials of probiotics have so far been limited in scope, and there has yet to be a systematic trial definitively demonstrating the role of probiotics in addressing or preventing mental illness. Nonetheless, the data so far have been supportive of a causal relationship between intestinal bacterial composition and mental health. With a greater understanding of the specific organisms responsible for contributing to these diseases, this research may enable microbial modulation (including the probiotic supplementation of protective bacteria) to become an alternative treatment modality in psychiatric illness.

Immunology

Given that the intestinal microbiome is involved in countless interactions with its host's immune system, the presence of a relationship between microbial composition and immunologic disease is unsurprising. The most established correlation has been in the context of inflammatory bowel disease (IBD). Organisms such as B. fragilis, segmented filamentous bacteria, and mucosal–adherent E. coli have been implicated in disease progression, primarily through toxin–mediated mucosal barrier disruption and pro–inflammatory mucosal invasion.[11-12] Treatments targeted at favourably shaping the flora have already been trialled in mouse models; treatment with low–dose penicillin in early life, aimed to specifically target the harmful segmented filamentous bacteria, was found to protect against the development of drug–induced colitis.[12] There has been a selection of other postulated IBD treatments targeted to work by similar mechanisms, including other specific antibiotics (including metronidazole), probiotics, and fecal transplant.[13] At this point in time, there has been no clear therapeutic advantage elucidated in human trials; however, there is considerable room for advancement in this field. Using a more precise approach and considering the specific factors in each patient's microbial profile may enable us to make more targeted efforts to therapeutically modulate the microbiome. Additionally, more research into the role of these microbial–modulating measures in healthy subjects may help identify those at risk for IBD development and ultimately lead to clinical benefit through prevention.

Oncology

The role of the intestinal microbiota in the pathogenesis of cancer is less well characterized and is still in the early stages of correlational studies. However, there have been several studies which have demonstrated the potential of the microbiome to promote a pro–inflammatory state, which in turn is known to be a predisposing factor for carcinogenesis. One notable example is hepatocellular carcinoma (HCC), which has been long known to have a significant association with chronic hepatic inflammatory changes and fibrosis. Given that the hepatic circulation receives the majority of its blood supply from the intestinal venous system, the liver is exposed to a high concentration of gut microbial by–products, including pro–inflammatory bacterial antigens and toxins.[14] An animal study conducted in mice with chronic hepatic injury demonstrated that exposure to common bacterial ligands (including lipopolysaccharide) suppressed apoptosis and promoted further proliferation in HCC tumours.[15] Furthermore, intestinal sterilization during hepatocarcinogenesis reduced overall tumour size by up to 70%, demonstrating the potential role of microbiological modulation in suppressing HCC development. Additionally, there have been many studies linking intestinal microbial architecture with colorectal cancer (CRC), implicating organisms such as S. bovis, B. fragilis, E. faecalis, and E. coli as being disproportionately represented in these patients' microbiomes.[16-17] Moreover, these populations have also been directly implicated in carcinogenesis; certain E. coli populations harbouring a DNA–damage–associated pks mutation, enriched in patients with CRC, have been found to promote colon adenocarcinoma proliferation.[18-19] Similar correlational studies have been done for pancreatic, lung, and squamous cell carcinomas. While there is still much more to be discovered before these study findings can be applied for therapeutic intent, this research is certainly laying the grounds for the exploration of targeted, microbe–specific approaches that may contribute to the prevention (or even treatment) of multiple forms of cancer.

Discussion

The balance of the microbiome has been shown to play a critical role in both the maintenance of health and the progression of disease across many fields of medicine. The key question that remains is whether this knowledge can be applied towards the prevention and management of these diseases. Analyzing each patient's microbial profile in order to identify contributory dysbiosis could offer new targets for therapy, as well as an opportunity to identify those at risk for developing disease. Microbial modulation may represent an entirely new frontier in the

expanding world of precision medicine, providing a new lens with which to guide individualized patient care.

However, much more research needs to be done before this approach could become a reality in the clinical world. To begin with, we need a more complete understanding of the specific microbial imbalances that may have a causal (or protective) role in disease before we can develop targeted treatments to address these factors. As previously discussed, the microbiome plays a critical role in normal physiology and disease prevention, so any intervention aimed at re–shaping the microbial balance could run the risk of disrupting its normal functions. Antibiotic treatments will need to be carefully considered, as the potential risk of impairing normal floral function (or more significantly, of enabling the notorious C. difficile infection) could outweigh the potential benefits of intervention. Furthermore, there is the issue of identifying patients whose microbial composition puts them at risk for various diseases. It is unclear which factors would prompt a physician to assess a patient for intestinal dysbiosis, and moreover, as of now, the tools with which this could be done (including genetic sequencing analysis from fecal samples) are unfamiliar, expensive and of questionable accuracy.[20] We would need to develop robust guidelines for identifying patients who would benefit from screening, as well as to standardize the analysis of microbial risk factors, whether this involves holistic sequencing of the entire microbial architecture or screening for biomarkers of pathogenic bacteria. Ultimately, this entire process would need to be subjected to the rigorous scrutiny of cost–effectiveness, as with every screening tool.

Conclusion

In short, as attractive as the microbiome is as a novel therapeutic target, there is still a significant amount of research that needs to be done before translating our basic understanding of its role in pathogenesis into clinical practice, both in identifying actionable microbial targets as well as in making these measures a practical reality. Nonetheless, given the strong evidence which has been gathered so far, we may well be looking at a future where a combination of antibiotics, probiotics, and specific microbial–targeted therapies could form its own unique branch of personalized medicine.

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Distinguishing neuromyelitis optica spectrum disorder from multiple sclerosis using magnetic resonance imaging techniques

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is a rare neuroinflammatory central nervous system disorder, characterized by astrocytopathy with secondary demyelination. NMOSD and multiple sclerosis (MS) have overlapping clinical manifestations, making NMOSD clinically challenging to distinguish. A highly specific serum antibody test is available that can distinguish NMOSD from MS, but it is not very sensitive to NMOSD. The similarity of NMOSD clinical and imaging features to those of MS, and the lack of awareness about NMOSD among physicians could lead to misdiagnosis. Distinguishing NMOSD from MS is important as prognosis and treatment options differ. Here, we will discuss myelin water imaging, an advanced quantitative magnetic resonance imaging technique to explore the pathology of lesional and normal–appearing tissues of MS and NMOSD. We will also review machine learning methods that automatically distinguish between the two diseases. Both techniques are actively being studied at the University of British Columbia.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare central nervous system disorder that typically presents with optic neuritis, longitudinally extensive transverse myelitis, and area postrema clinical syndrome.[1] It is characterized by an antibody–mediated attack on water channels expressed on astrocytes and in the ensuing inflammatory response, secondary demyelination occurs.[1] Due to similar clinical manifestations, NMOSD was thought to be a subtype of multiple sclerosis (MS), which is an autoimmune disorder of the brain and spinal cord characterized by edema, inflammation, demyelination and axonal damage, resulting in impaired saltatory conduction.[2] Examples of these overlapping clinical symptoms include vision loss, weakness in extremities, fatigue and sensory dysfunction. However, NMOSD has emerged as a distinct disorder from MS since the discovery of serum aquaporin 4 immunoglobulin G antibodies (AQP4–IgG) in 2004.[3,4] This autoantibody marker is very specific (97-99%) to NMOSD; however, it is not as sensitive (59-76%).[4] This means that some patients who test seronegative for AQP4–IgG may still have NMOSD. Therefore, other imaging biomarkers or differentiation techniques are highly desirable to classify NMOSD from MS. The similar clinical and imaging features of NMOSD and MS, and the lack of awareness about NMOSD among physicians could lead to misdiagnosis, especially if the patient is AQP4–IgG seronegative with the presence of brain lesions. Differentiating NMOSD from MS has crucial implications to prognosis and treatment because standard MS therapy, such as interferon-beta, may worsen NMOSD and increase relapses.[5]

To better understand the different pathology of NMOSD and MS, magnetic resonance techniques can be used. Magnetic resonance imaging (MRI) is a non–invasive medical imaging tool that utilizes a strong magnetic field to align or anti–align magnetic moments of protons (termed spins), mainly from water, and use radio frequency pulses to manipulate the spins, generate signal, and produce images with high spatial resolution.[6] Conventional MRI is frequently used in diagnosis and clinical management of NMOSD and MS. It is useful for visualizing lesion distributions in space and time. However, the limitations of this imaging modality include low specificity to pathological processes, low sensitivity to diffuse damage in the normal-appearing white matter, and limited association with clinical status in both MS and NMOSD.[7] Therefore, there is significant ongoing research into using advanced MRI techniques to better understand pathological processes such as demyelination and axonal loss in disease–specific tissues. Here, we discuss myelin water imaging, which can be used to investigate the differences in pathological processes in both lesional and normal–appearing tissues of NMOSD and MS, as well as machine learning approaches that are used to automatically distinguish between NMOSD and MS for early and accurate diagnosis of NMOSD. Both techniques are currently actively studied at the University of British Columbia.[8-13]

Myelin Water Imaging

Myelin is a fatty substance that envelops the axon and enables saltatory conduction, allowing increased conduction velocity.[14] Damage to myelin slows the transmission of information sent along the axon and causes the exposed axon to degenerate. Therefore, a measurement of myelin content *in vivo* can be useful in better understanding demyelinating diseases such as MS and NMOSD.

Myelin water imaging (MWI) is an advanced, quantitative MRI technique that was developed and pioneered by Dr. Alex MacKay's group at the University of British Columbia in 1994.[15] MWI uses multi–echo T2 relaxation measurements to quantify the fraction of signals originating from three major water compartments in healthy human brain: a long T2 (~2 sec) from cerebrospinal fluid, an intermediate T2 (~60-80 msec) from intra– and extracellular water, and a short T2 (~15-20 msec) from water trapped between the myelin bilayers.[6,15,16] The myelin water fraction (MWF) is defined as the ratio of water between myelin bilayers to the total water content.[6] Furthermore, the MWF has been validated as a marker for myelin content by histopathological analysis using a myelin–specific stain in postmortem human brain tissues.[17] Since its validation, many studies have focused on MWF to better understand MS and NMOSD pathology.

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In 2016, Jeong et al. compared the MWF in periventricular white matter lesions in 27 relapsing–remitting MS and 20 AQP4 IgG-positive NMOSD patients, as periventricular white matter is commonly affected in both conditions.[18] They found that the mean MWF in MS periventricular lesions (4.06±2.69%) was significantly lower than in NMOSD periventricular lesions (6.18±3.15%) (p=0.002).[18] Furthermore, they found that 59.4% of the MS lesions, compared to 33.3% of the NMOSD lesions, had severe (≥75%) myelin loss (p=0.001), thereby suggesting that there is more severe demyelination in MS than in NMOSD.[18] However, Jia et al.[19] noted that the data must be interpreted with caution, as MWF was reported to vary among different lesion types in MS.[20]

Additionally, Matthews et al. found several normal-appearing white matter regions with significant MWF reduction in the MS cohort over one year; however, this change was not seen in NMOSD or controls.[21] Therefore, there were widespread neurodegenerative changes in MS but not NMOSD cohorts, which may support the clinical finding of progression in MS but little or no progression in NMOSD.[21]

In contrast to studies done by Jeong et al. and Matthews et al., a combined transcranial magnetic stimulation (TMS) and MWI study showed lower TMS recruitment curve slopes and lower MWF in the corticospinal tract in NMOSD, compared to MS and controls. This suggested greater damage in NMOSD than in MS.[13] The conflicting results may be due to small sample size and different patient population, particularly since the disease course of MS is very heterogeneous.

Currently, there is active research focusing on myelin water imaging at the University of British Columbia. For example, Combes et al. investigated potential diffuse myelin changes in NMOSD by computing z-score MWF maps from a MWF atlas that was created from healthy control data.[8] This illuminated how much MWF in NMOSD deviated from the normal.[8] They found that the volume of abnormal MWF in MS (378±542 voxels, p=0.001) and NMOSD (126±205 voxels, p=0.1) were higher than in healthy controls (33±65 voxels).[8] Furthermore, lesion volume was significantly correlated with volume of abnormal MWF (p=0.02) and average normal–appearing white matter z-score (p=0.009) in MS; however, this pattern was not detected in NMOSD.[8] In the future, further longitudinal studies with larger datasets investigating the difference in MWF in brain and spinal cord lesions and normal–appearing white matter are warranted.

Finally, even though MWF has been shown to correlate with histological stains of myelin,[17] there are some confounding factors that may affect *in vivo* measurement of MWF. For example, after myelin damage in MS and NMOSD, macrophages clear myelin debris from the injury site. If the myelin debris is not cleared efficiently, it may affect MWF. Animal studies have shown that myelin debris may affect MWF;[22-24] however, this has not been studied in human tissues.

Machine Learning Approach

Machine learning-based pattern recognition techniques have advantages over human observation, such as their ability to take a large number of variables into consideration and improve classification with consistency.[25-32] Additionally, this predictive approach of using machine learning can help to better differentiate NMOSD and MS in a way that it is reproducible and interpretable. Recently, this technique has gained much popularity in psychiatric disorders[26,27] and neurodegenerative disorders such as Alzheimer's disease,[25,28] traumatic brain injury,[29] and clinically isolated syndromes.[30]

In 2015, Eshaghi et al. used a machine learning algorithm on support vector machines, and found that the average accuracy to differentiate NMOSD and MS was 88% using both conventional and advanced imaging techniques.[31] Here, white matter lesion load, normal–appearing white matter integrity, and functional connectivity were the most important factors for distinguishing between NMOSD and MS.[31] A limitation of this study was that it was conducted at a single centre, thereby failing to ensure generalizability of its model to a global patient population.

Therefore, in 2016, Eshaghi et al. used a random–forest, which is another machine learning algorithm for classification, from two sites, using only conventional imaging techniques.[32] They found that the cortical thickness, volume, and surface area measures resulted in average accuracy, sensitivity and specificity of 74%, 77% (i.e., 77% of true MS cases were classified as MS), and 72% (i.e., 72% of true NMOSD cases, without MS, were correctly classified), respectively, to distinguish between MS and NMOSD.[32] When they combined thalamic volume, the most discriminating gray matter measure, with white matter lesion volume, it resulted in higher average accuracy, sensitivity, and specificity of 80%, 85% and 76%, respectively between NMOSD and MS, in two sites.[32] Given these results, a machine learning approach that automatically differentiates NMOSD from MS would be advantageous as the main method for differentiating between the two diseases. In comparison, the AQP4-IgG serum test method is highly specific (97-99%) but not as sensitive (59-76%).[4]

Currently, researchers from the University of British Columbia are developing a machine learning algorithm to distinguish NMOSD from MS as well.[9] The aim is to use a machine learning approach based on artificial neural networks, called deep learning, to determine if the patterns of brain MRI lesions and measures derived from diffusion tensor imaging (DTI) can automatically discriminate between NMOSD and MS.[9] DTI is a quantitative MRI technique that measures characteristics of water diffusion and it is influenced by—but not specific to—myelin content, axonal damage, inflammation or edema.[6] Preliminary results on 82 NMOSD and 52 MS patients have shown that deep learning can achieve an accuracy rate of 81%, thereby demonstrating the potential of deep learning to distinguish NMOSD from MS using patterns of brain lesions and diffusion tensor imaging metrics.[9] A limitation of the machine learning method is that it is not a hypothesis–driven approach. Instead, it reveals relationships upon receiving large amounts of information, but it cannot guarantee these are causal relationships. In the future, the machine learning approach can be further studied to differentiate NMOSD with and without AQP4-IgG.

Conclusion

Although conventional imaging is useful in the diagnosis and clinical management of neuroinflammatory diseases such as NMOSD and MS, it faces limitations including low specificity to pathological processes, and limited association with clinical status in MS and NMOSD. Quantitative MR measures can provide valuable information on pathology and can be used to develop machine learning algorithms to facilitate earlier and more accurate diagnosis of NMOSD automatically. Myelin water imaging can successfully detect the differences in myelin content between lesional and normal–appearing NMOSD and MS tissues. Therefore, MWI can provide insight on disease progression and treatment efficacy. Furthermore, machine learning–based pattern recognition techniques using gray matter measures alone or in combination with white matter lesion load, as well as DTI metrics, have

the potential to distinguish NMOSD from MS automatically. All these techniques may facilitate earlier and accurate differential diagnosis in clinical practice.

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Visual hallucinations in patients receiving intravitreal anti–VEGF agents in northern British Columbia: Prevalence and characteristics

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Abstract

Objectives Visual hallucinations, also known as Charles Bonnet Syndrome, are sometimes experienced by patients with poor vision. The aim of this study was to determine the prevalence and characteristics of visual hallucinations in adult patients receiving intravitreal anti–vascular endothelial growth factor (VEGF) treatment for macular degeneration, diabetic retinopathy, and retinal vein occlusion (RVO).

Study Design Cross-sectional survey.

Methods Participants with poor vision were recruited from an anti–VEGF injection clinic for treatment of age–related macular degeneration (AMD), diabetic retinopathy, and RVO. Anti–VEGF agents included bevacizumab, ranibizumab, and aflibercept. Patients were screened for visual hallucinations, and vision was tested (best corrected visual acuity and contrast sensitivity).

Results 122 patients (mean age 75.3 years) were screened in a period of 6 weeks. 49 were male (40.2%). Diagnoses included AMD (n=92; 75.4%), diabetic retinopathy (n=21; 17.2%), and RVO (n=17; 13.9%). The prevalence of Charles Bonnet syndrome was 6.6% (n=8). Hallucinations usually involved images of people, were brief (<30 s-10 mins), and were associated with dim lighting (n=6). Poor visual acuity (p=0.002) and contrast sensitivity (p=0.001) were associated with visual hallucinations.

Conclusions Patients who see an ophthalmologist for treatment of eye diseases (macular degeneration, diabetic retinopathy, and RVO) can experience visual hallucinations that do not have a mental illness genesis. Patients will benefit from increasing health care professionals' awareness of Charles Bonnet syndrome, as hallucinations can be associated distinctly with poor visual acuity and contrast sensitivity, rather than secondary to mental illness.

Abbreviations CBS – Charles Bonnet Syndrome; VEGF – vascular endothelial growth factor; AMD – age-related macular degeneration; RVO – retinal vein occlusion

Introduction

Charles Bonnet Syndrome (CBS) was first described by Swiss philosopher Charles Bonnet in the 18th century. He noted visual hallucinations in his grandfather, who was blind secondary to cataracts.[1] Bonnet described three key elements still used in modern clinical practice: patients with CBS experience visual hallucinations with preserved insight, have low vision secondary to eye disease, and have intact cognition.[1-3] CBS is commonly experienced by elderly patients, between 70-85 years old[3,4], who have poor vision, yet clinicians and patients remain largely unaware of the diagnosis. The pathogenesis of CBS is uncertain, though two main theories exist. The "release theory" suggests that the visual cortex receives abnormal signals from a lesion in the visual pathway, leading to hallucinations.[5] Alternatively, the "deprivation theory" suggests that the visual association cortex produces images due to a reduction in sensory input.[3,5]

Reported visual hallucinations can be quite varied in their description, but commonly experienced hallucinations do not last more than a few minutes and include patterns, faces, objects, figures, and animals.[3] Hallucinations can be in colour or greyscale, and images can be moving or stationary. Other characteristics remain under study, as current studies report contradicting results regarding the effects of sex, living arrangements, light, time of day and other factors on the prevalence of CBS. Advanced age and low visual acuity have been shown to be risk factors for CBS, especially in patients who have advanced macular degeneration (AMD).[6,7] Poor contrast sensitivity is another known risk factor for CBS.[8] Other eye diseases such as glaucoma, diabetic retinopathy, RVO, and cataracts are seen in patients with CBS.[2,3,5,7-9]

The prevalence of CBS in elderly patients is reported to be anywhere from 0.5-40%.[1,5,10] The high variance in rates of CBS can be attributed to the association of visual hallucinations and mental illness. Case reports have noted that patients can feel distress, and many do not seek medical advice for fear of diagnosis with mental illness or neurodegenerative diseases such as Alzheimer's dementia.[11] As much as 60% of patients experience confusion during visual hallucinations and 33% were fearful of impending insanity.[5] As such, it is important to clarify with patients that visual hallucinations are not always related to cognitive dysfunction.

The purpose of this study will be to determine the prevalence of visual hallucinations in patients receiving intravitreal anti–vascular endothelial growth factor (VEGF) treatment in Prince George, British Columbia. It will also be possible to determine characteristics of any hallucinations experienced, such as description, onset, and triggering factors. This information can aid in our current understanding of CBS.

Methods

This clinic–based study was undertaken in Prince George, a community in northern British Columbia. This population was chosen for sampling convenience (proximity to researchers, as well as common eye pathologies among participants). Participants over 18 years of age receiving treatment for AMD, diabetic retinopathy, and RVO were recruited through an injection clinic. All participants were receiving anti–VEGF agents (bevacizumab, ranibizumab, or aflibercept). Anti–VEGF agents help to preserve vision by preventing the formation of leaky blood vessels and

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edema. Over a period of 6 weeks, 122 patients gave informed consent to participate in the survey. Ethics approval was obtained from UBC Behavioural Research Ethics Board (ID=H15-02003).

Each patient was given a one–to–one short introduction to Charles Bonnet Syndrome. Patients were informed that people with poor vision like themselves can experience visual hallucinations, and that these hallucinations might not necessarily be caused by mental illness. Hallucinations were defined as concrete images without a stimulus. Thus, other visual disturbances such as scintillations, illusions, and distortions were excluded based on history. Patients who screened positive for visual hallucinations were asked further questions to describe their experiences. A standardized questionnaire explored the content of hallucinations, as well as onset, duration, frequency, triggers, and temporal relation to anti–VEGF treatment. All questionnaires were verbally administered by the same study researcher.

Patients were asked about their general medical health and were screened for a history of hypertension, stroke, migraines, diabetes mellitus, depression, schizophrenia, Parkinson's disease, and dementia. Diagnoses of ocular pathologies and best corrected visual acuity (binocular) were obtained directly from the patients' charts.

Finally, binocular contrast sensitivity testing was undertaken using a validated iPad contrast sensitivity test created by Ridgevue.[12] An iPad with retinal display was placed one metre away from the patient with the room lights off. The auto–brightness was turned off, and the brightness was adjusted to the middle of the scale. Each page of the test consists of two letters of equal contrast, and the contrast of subsequent pages decreases by 0.1 log units. Testing ended when the patient missed both letters on a given contrast page. Contrast sensitivity was scored as 0.05 x total number of correct letters.

A stepwise multiple linear regression analysis was used to develop a model for predicting Charles Bonnet Syndrome from vision code, contrast sensitivity, age of patients, RVO, diabetic retinopathy, cataracts, AMD and patient sex. Statistical significance was defined as p–value≤0.05. Best corrected visual acuities were stratified based on overall functionality (Canadian National Institute of the Blind vision code 0 = 20/20 to 20/69; vision code 1+ = 20/70 or worse).[7] Characteristics of visual hallucinations were tabulated.

Table 1 | Prevalence of Charles Bonnet Syndrome, demographics.

	Number (%)	Number with Hallucinations (%)
Total Clients	122 (100)	8 (6.6)
Age		
>80	47 (38.5)	6(75)
65-80	54 (44.3)	2 (25)
<65	19 (15.6)	0
Sex		
Male	49 (40.2)	3(37.5)
Female	73 (59.8)	5(62.5)
Ocular Pathology*		
AMD	92(75.4)	7(87.5)
Cataracts	3(2.5)	0
Glaucoma	8(1.6)	1(12.5)
Diabetic Retinopathy	21(17.2)	0
Retinal Vein Occlusion	17 (13.9)	1(12.5)

*Patients can have more than 1.

Table 2 | Correlations between Charles Bonnet Syndrome and predictive factors.

	Charles Bonnet Syndrome	P value
Vision Code 1+ (20/70 or worse)	0.25	0.002
Contrast sensitivity	-0.31	0.001
Sex of Patient	0.02	0.411
AMD	0.15	0.047
Cataracts	-0.04	0.322
Diabetic Retinopathy	-0.12	0.105
Retinal Vein Occlusion	-0.012	0.449

Results

Out of 122 clients, 49 were male (40.2%). Average age of participants was 75.3 years. Diagnoses included AMD (n=92; 75.4%), diabetic retinopathy (n=21; 17.2%), and RVO (n=17; 13.9%). Out of 122 clients, 8 met the diagnostic criteria for Charles Bonnet Syndrome (prevalence rate of 6.6%). Demographics of the patient cohort is shown in Table 1. Higher vision code (poor visual acuity; p=0.002) and poor contrast sensitivity (p=0.001) were significant predictors of Charles Bonnet Syndrome. The one–predictor model was able to account for 6% of the total variance in Charles Bonnet Syndrome, F(1, 117) = 8.01, p<.01, R2=0.06, 95% CI [0.02, 0.14]. Further correlations between Charles Bonnet Syndrome and predictive factors can be found in Table 2.

In the cohort which screened positive for visual hallucinations (n=8), the quality of the hallucinations were explored (see Table 3). The most common hallucination experienced was that of people and faces (n=7). There was a mixture of chromatic and greyscale, although most participants had stationary hallucinations (n=7). Hallucinations tended to be brief (<30 seconds to 10 minutes), and often occurred in situations with dim lighting (n=6). The onset of hallucinations ranged from 1+ months to several years. Very few participants (n=2) had previously discussed their experiences with a physician.

Discussion

The findings in this study are congruent with past studies, and confirmed that visual hallucinations are not uncommon in patients with low visual acuity. The overall prevalence rate was 6.6%, which is lower than the rate of 18.8% seen in a recent large CBS cohort study.[7] The high variance in rates of CBS can be attributed to the association of visual hallucinations and mental illness, and it is possible that some patients were hesitant to disclose. Past studies reported a prevalence of CBS to be anywhere from 0.5 to 40%.[1,5,10]

The findings in this study also suggest that visual hallucinations are associated with both poor visual acuity and poor contrast sensitivity, which is consistent with past studies.[6-8] These findings also support one of the proposed etiologies of CBS, known as deprivation or deafferentation theory. Poor visual acuity and poor contrast sensitivity can contribute to sub–threshold visual input, which causes the visual association cortex in the brain to produce images—visual hallucinations.[3,5] Although the underlying etiology of CBS remains unclear, the finding that there was no difference in the prevalence of CBS in each eye pathology suggests that the vision loss itself plays a bigger role in the etiology of visual hallucinations.

By exploring the quality of visual hallucinations in our small cohort of 8 people, a wide variety of visual hallucinations were seen. All 8 patients confirmed that they experienced hallucinations prior to starting anti–VEGF treatment. The most common hallucination experienced was that of people and faces, and usually these hallucinations were stationary.

Table 3 | Characteristics of hallucinations experienced in Charles Bonnet Syndrome.

Hallucination Characteristics	Patient 1 82 yo F	Patient 2 78 yo M	Patient 3 84 yo F	Patient 4 84 yo F	Patient 5 72 yo M	Patient 6 89 yo F	Patient 7 84 yo M	Patient 8 83 yo F
Ocular pathology	AMD, glaucoma	AMD	AMD	AMD	AMD	AMD, detachment 25 years ago	AMD	Central RVO
Visual Acuity in best eye (score)	20/50	20/400	Hand motions	20/25	20/40	20/200	20/50	20/100
Contrast sensitivity	0.65	N/A	0.9	1.5	1.5	1.1	1.4	1.05
Description of hallucinations	People	People and faces (cartoonish)	Shapes	People (elf–like)	People (sometimes familiar)	Faces only	People (sometimes half body)	People (half body)
Onset	2-3 years ago	1 year ago	6 months ago, have stopped	1+ months ago	3-4 months ago	5 years ago. Stopped 1 year ago	6 months ago	6 months ago
Duration	1-2 mins	1 min +	2-3 mins	<30 seconds	3-10 mins	2-3 minutes	4-5 seconds	Few seconds to few minutes
Frequency	1-2x per week	Up to 10 per day	2-3 per day	Twice	Unable to quantify	1 per month	1 every 2 weeks	1 every 3-4 weeks
Chromatic or Greyscale	Both	Colour	Colour	Colour	Greyscale	Greyscale	Greyscale	Both
Moving or Stationary	Stationary	Stationary	Stationary	Stationary	Moving	Stationary	Stationary	Stationary
Triggers	Dim lighting	When trying to focus	Dim lighting	None	Dim lighting	Dim lighting	Dim lighting	Dim lighting
Recreational Drug Use	Oral marijuana (hallucinations 1 year before use)	No	No	No	No	No	No	No
Discussed with others previously	No	With physician	No	With daughter	With physician, wife	No	No	Family members
Degree of distress	Initially, none now	None	Initially, none now	A little distress at time	Some distress	None	None	None

Hallucinations tended to be brief (minutes in duration). Dim lighting was a notable trigger in our CBS cohort, which supports deprivation theory. Because these patients had been experiencing hallucinations for an extended period of time (months to years), they did not report significant distress when hallucinations recurred. However, all patients reported feeling relieved when they were reassured that visual hallucinations can be a consequence of their vision loss. Interestingly, very few participants had previously discussed their experiences with a physician. This suggests that there is still a stigma with mental illness.

Research limitations

Although efforts were made to screen for other causes of visual hallucinations, including mental illness, it is possible that some patients who met the criteria for Charles Bonnet Syndrome might in fact have another underlying cause of hallucinations other than poor visual acuity and contrast sensitivity. As discussed previously, it can be difficult to determine the true prevalence rate of CBS due to the inherent stigma of mental illness. As a result, it is possible that some patients were reluctant to disclose that they were actually having visual hallucinations. It was hoped that this reluctance would be minimal due to the time spent in explaining CBS to each patient.

In hindsight, it would have been beneficial to explore whether or not visual hallucinations preceded low or reduced vision. In addition, this study had a relatively small sample size, a very specific patient population, and is only limited to northern British Columbia.

Conclusion

The findings in this study are congruent with past studies, and confirmed that visual hallucinations are common in patients with low visual acuity. Many elderly patients with poor visual acuity can experience hallucinations, and thus it is important to increase the awareness of Charles Bonnet syndrome in the medical community in order to improve patient care. Healthcare providers have a great capacity to inform patients that visual hallucinations are not always associated with mental illness. In addition, appropriate referrals can be made to other healthcare professionals to rule out other conditions that can cause visual hallucinations.

There appears to be an association between poor contrast sensitivity and visual hallucinations. Although the etiology of CBS remains unclear, it is possible that contrast sensitivity can play an important role in the etiology of visual hallucinations (deprivation theory). Currently, there is limited research in this field, and future research endeavours might be beneficial in furthering our understanding of visual hallucinations. It would also be beneficial to further explore patient perspectives on visual hallucinations in the future.

Footnotes and disclosure

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