Title
Examining the Interaction of Genes and Epidemiology on Castleman Disease

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Abstract

Castleman Disease is a rare disorder in which a person experiences an overgrowth of cells in the lymph nodes. Research on Castleman Disease is, at the moment, very elementary due to the lack of patient population size and previous research. Currently, the only research on Castleman disease covers understanding classifications of the disorder, possible causes ranging from immune deficiencies to cytokines, and genetics (Jiang et al., 2020). Because of the disease's rarity, scientists have not conducted much research; thus, there is still no cure for this disease, and its cause is largely unknown. We analyzed research publications from sources such as PubMed, Google Scholar, and NIH. This paper will study the development of Castleman Disease in relation to the interplay between genetic and epidemiological factors, as evidenced by the associations between Castleman Disease and specific DNA mutations, HIV, and HHV-8.

Key words: Castleman Disease, epidemiology, genetics

Introduction

First discovered by Dr. Benjamin Castleman in 1954, Castleman Disease (CD) is a rare heterogeneous cluster of disorders characterized by the overgrowth and enlargement of lymph node cells in the body. Lymph nodes and lymphocytes (white blood cells within the lymph nodes) are essential to our immune system to help fight against infections and disease in the body. But in CD, these lymph nodes undergo mutations, causing the increased production of these white blood cells and proteins. This disease is classified by how far it spreads throughout the body. The two main forms of CD are Unicentric/Localized Castleman Disease (UCD) and Multicentric Castleman Disease (MCD), which include subtypes of HHV-8 Positive MCD and Idiopathic MCD. Based on treatments, patients diagnosed with UCD have an average survival rate greater than 10 years, and seems to have little effect on one's life expectancy. However, MCD can be life threatening with a 35% fatality rate within 5 years (Dispenzieri et al. 2012). As of 2019, it is estimated that 6,500 - 7,700 patients are diagnosed with Castleman Disease in the United States and can affect people of any age, gender, and ethnicity (Cleveland Clinic, 2019). Because of its rarity, many cases of Castleman Disease go misdiagnosed or delayed.

Unicentric Castleman Disease makes up 75% of Castleman Disease cases (Kaur et al. 2015). UCD occurs when there is an abnormal overgrowth of cells in the lymphatic system. Unicentric Castleman disease only affects a single group of lymph nodes and is not widespread throughout the body—often making it simpler to treat. The lymph nodes most affected by UCD are located in the chest or abdomen. Due to the enlarged lymph nodes, the patient may experience breathing problems because of pressure on the trachea or bronchi, abdominal pain, or difficulty eating. UCD is most often treated by surgical removal of the affected lymph nodes as only a specified area is primarily affected by the disease.

Though a majority of cases are identified as UCD, the second most diagnosed is Multicentric Castleman Disease. MCD affects the lymph nodes in a systematic manner, involving multiple different regions of lymph nodes. Symptoms for MCD can range from mild to life-threatening; including fever, weight loss, rash, enlarged liver, spleen, and enlarged lymph nodes. Human Herpesvirus-8, or HHV-8, associated MCD makes up about half of the cases of MCD. It is thought that multiple infections of the lymph nodes provokes a high release of cytokines (inflammatory chemicals) that ultimately cause the symptoms seen in MCD (NORD, 2017).

Idiopathic Multicentric Castleman Disease, or iMCD, on the other hand, lacks a true known origin. The HHV-8 aspect that characterizes MCD is absent in iMCD. Speculation about causes of iMCD range from possible infection from a virus other than HHV-8, genetic mutations, inheritance of a genetic mutation, and autoimmunity; however it is known that patients have the same high level of cytokines seen in MCD patients and experience the same symptoms. To understand MCD and iMCD, it is crucial to address HIV and HHV-8 (*Castleman Disease,* 2020).

In this literature review, we will examine publications to provide an explanation for Castleman Disease in relation to two other diseases, HIV and HHV-8, that are often correlated with it. Then, we will discuss the possible causes of Castleman Disease and conclude that the development of this disease is likely due to a combination of genetics and diseases which can exacerbate the progression of Castleman Disease. We hypothesize that the development of Castleman Disease may be enhanced through environmental factors, as evidenced by the associations and correlations between CD, HIV, and HHV-8.

Methods

To further our understanding and research on the environmental and genetic roots of Castleman Disease, we conducted a search of current literature and research publications, particularly focusing on scientific databases such as CDC, NIH, PubMed, and other credible publishers. To find the relevant papers, the search criteria centered around the following questions: What are the genetic predispositions of Castleman Disease? How do epidemiological factors affect Castleman Disease? How does the interaction between genes and epidemiology influence the development of Castleman Disease?. In particular, the key terms searched included "multicentric/unicentric Castleman Disease", "genetic mutations Castleman Disease", "environmental factors Castleman Disease", "MCD and HIV/HHV", among other appropriate terms relevant to this paper. We narrowed down our search by focusing on sources published between 2010 to present 2022 to get the most recent research. Moreover, we delved deeper into the work of Dr. David Fajgenbaum, a physician at the University of Pennsylvania Perelman School of Medicine, renowned for his research regarding Castleman Disease. Dr. Fajgenbaum himself is a patient battling with idiopathic Multicentric Castleman Disease (iMCD), and his drive to find a cure led him to co-found the Castleman Disease Collaborative Network (CDCN), "dedicated to accelerating research and treatment for Castleman disease" according to its website (CDCN, n.d.). The sources we acquired include primary sources that report original data and information based on original studies conducted by the researchers, secondary literature reviews on the genetics and epidemiological factors associated with CD, as well as information from credible government/non-profit websites. Overall, we compiled and analyzed information from eighteen sources.

Results

Genetic Correlation

With more emerging research on Castleman Disease, significant genetic mutations and abnormalities are being associated with Castleman Disease.

Abnormalities in Chromosome 7

One of the most recurring chromosomal abnormalities among CD patients was of Chromosome 7 in comparison to other chromosomes (Figure 1). Researchers noted two cases of translocation (when the chromosome breaks and reattaches to a different chromosome), two cases of additional material of unknown origin, and even chromosomal deletion occurring in two cases with Unicentric Castleman Disease (Butzmann et al., 2021).

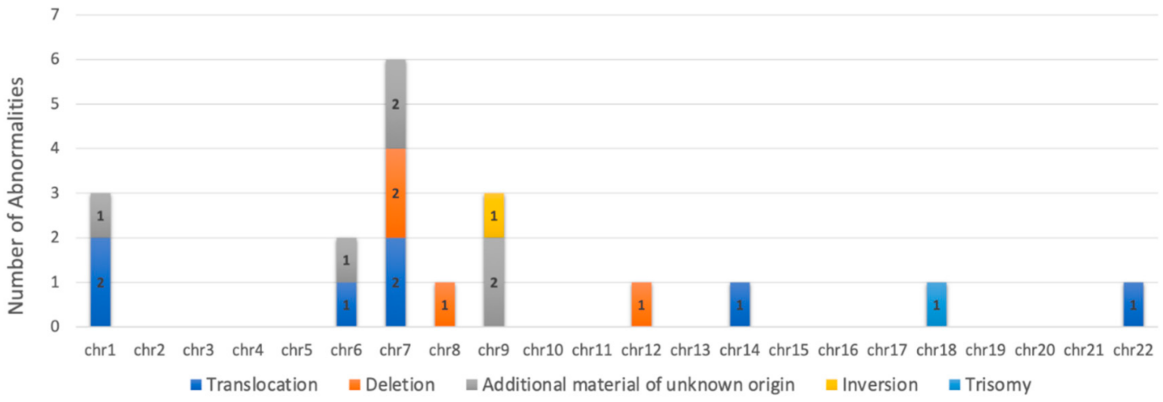

Figure 1. *Highlights the number of genetic abnormalities of chromosomes reflected in patients with Castleman Disease.*

Specific Point Mutations

When performing genetic sequencing on 41 patients, researchers identified 1034 non-silent amino acid mutations in somatic cells, and have discovered that the platelet-derived growth factor receptor beta gene (PDGFRβ gene) in the lymphatic cells was the most frequent gene mutation in 7 of 41 patients (17%) diagnosed with UCD in the study (Butzmann et al., 2021). When compared to different forms of cancer, the PDGFRβ mutation in stromal cells

occurred at a higher prevalence rate for UCD patients (Figure 2), strongly indicating that this genetic link is vital to better understanding the probably causes of UCD (Li et al., 2019).

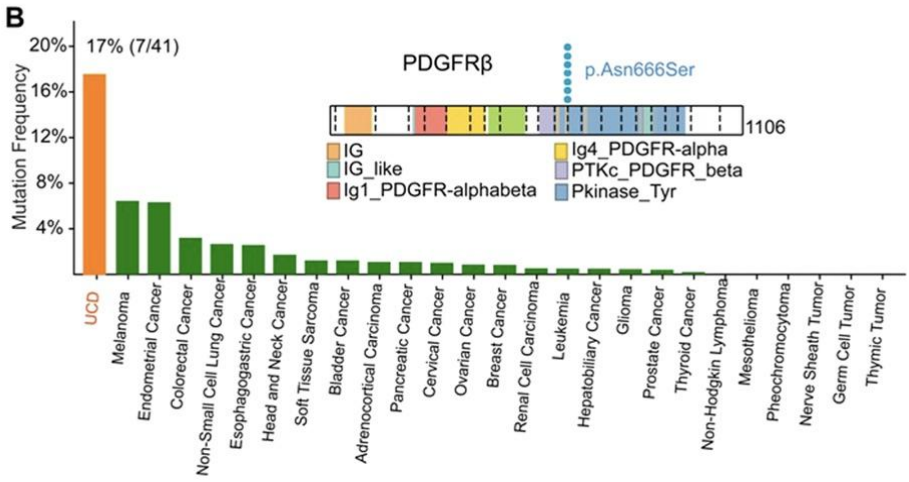

Figure 2. *Image B shows the increased prevalence of PDGFRβ mutation in CD patients compared to various forms of cancer.*

FAS Mutation

Another notable case study was on a family of four, where two members were diagnosed with CD. One was the father who was diagnosed with UCD at the age of 62. The other was the son diagnosed with iMCD at the age of 23. The mother and daughter of the family were both diagnosed with breast cancer. Through whole-genome sequencing of the father, son, and daughter it was found that the highest ranked genetic variant was a substitution that had occured in the FAS gene, where arginine was replaced with glycine at position 68. This variation has never been reported before in the Genome Aggregation Database. Moreover, even though the daughter had the FAS mutation, she reported no symptoms of CD. FAS is crucial for maintaining homeostasis in the lymphoid organs and providing instructions to make protein involved in cell signaling. It is important to note that despite both the father and son having the same genetic mutation, the father had symptoms at an older age whereas the son suffered from CD early on. Thus, it is clear that although genetic mutations with a link to CD may be inherited, other genetic

or environmental factors play a role in influencing the occurrence of Castleman Disease in the family (Baker et al., 2018).

With current research, it is more evident that genetic mutations in both Unicentric CD and Multicentric CD are not inherited, but rather acquired throughout one's lifetime and often influenced by environmental or epidemiological factors.

Epidemiological Factors

Background

Human Immunodeficiency Virus

While UCD has more established protocols for treatment, little is known about MCD and iMCD pathogenesis, making treatment development difficult. However, there has been shown to be an association between MCD and more researched diseases like HIV and HHV-8 providing an avenue for further understanding of MCD through assessing its relation to these other diseases. Human Immunodeficiency Virus (HIV) is an infection that deteriorates the body's immune system by destroying CD4 T-cells, white blood cells that play an integral role in fighting disease. HIV is a sexually transmitted infection, but may also be passed from person to person through other means, such as contact with infected blood (World Health Organization, n.d.). It is important to consider the association between HIV and MCD, as many MCD cases are also positive for HIV as well as HHV-8, raising questions as to whether an exploration of this association may provide a greater understanding of MCD pathogenesis and potential treatment.

Human Herpesvirus-8

The association between Human Herpesvirus-8 (HHV-8) and MCD is also crucial in understanding possible causes of MCD. The HHV-8 virus causes lesions to grow throughout various parts of the body and can cause cancerous growths as well. In fact, some scientists

believe that HHV-8 can directly cause MCD, indicating that MCD may be environmentally acquired (at least in some cases). There is still, however, a great deal of uncertainty surrounding MCD. Perhaps HHV-8 simply increases a person's chance of acquiring MCD rather than causing it. Or perhaps there is a genetic link between HHV-8 and MCD. This paper hopes to address the complicated development of both Unicentric and Multicentric Castleman Disease through the outlook of epidemiology below.

Mechanism

HHV-8 has been identified as a major player in MCD pathogenesis, possibly causing about half of MCD cases. A simplified model for how HHV-8 can cause MCD states that HHV-8 infected cells secrete a substance known as viral interleukin-6 (vIL-6). This induces the production of Vascular Endothelial Growth Factor (VEGF) which causes further swelling of the lymph nodes, progressing MCD (Hazem et al., 2011).

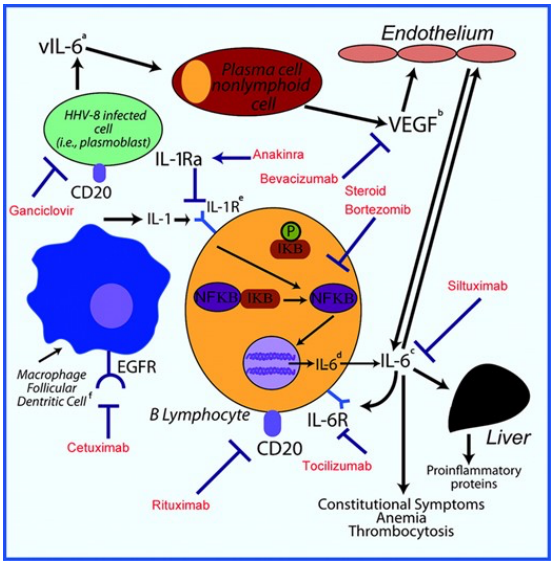

Figure 3. *This diagram shows a more complex version of how HHV-8 can cause MCD.*

The primary association between HIV and MCD is that patients positive for HIV present higher frequencies of also having HHV-8 associated MCD, as their immune system is weakened from HIV and thus unprepared to fight off an HHV-8 infection. This leads to poorer prognosis in

these patients than HIV patients without MCD (Krause et al., 2014). The interplay between these three viruses suggests that epidemiological factors play an important role in the development of MCD. HIV can be transmitted between individuals as a sexually transmitted infection or through infected blood on shared needles or other devices, factors purely environmental rather than genetic. Because HIV infection is heavily associated with MCD, patients may thus develop MCD through epidemiological means.

Of course, this research does not insist that MCD can only be caused by epidemiological factors. There could be genetic links behind this disease that are still largely undiscovered. However, research surrounding the correlation between HHV-8 and MCD is especially interesting when trying to assign a cause to MCD. As mentioned earlier, the pathway from HHV-8 to a growth factor which can progress MCD highlights that HHV-8 can further develop MCD; but this is not proof of causation. Another interesting piece of evidence is that the quantity of HHV-8 in plasma increases during MCD flares (Reddy et al., 2011). Additionally, HHV-8 replication is extremely high in infected cells of a patient with MCD (Reddy et al., 2011). However, both these correlational pieces of evidence do not prove causation. The only concrete evidence this provides is that an HHV-8 infection can cause MCD to progress faster. However, further research may be able to assign a HHV-8 as a direct cause of MCD.

Environmental Influences

Though there is no true evidence of environmental factors that are the cause of Castleman Disease, it is possible to hypothesize a few. First, simultaneous infection of viruses during an immunosuppressive state can activate HHV-8 and further promote the development of MCD (Guerrero et al., 2019). Additionally, as humans age, immune deficits are more likely to lead to HHV-8 (Dossier et al., 2013). A study done to test the effectiveness of rituximab treatment for

MCD provided further evidence of age-related high association of HHV-8, specifically in the Mediterranean regions. Individuals who are diagnosed with Castleman Disease and HHV-8 associated with HIV are increasing in number in aging patients, suggesting that aging may bring loss of control over immunity towards HHV-8. There is continuous evidence that age may play a factor in the development of Castleman Disease.

Castleman Disease is additionally associated with other issues ranging from anemia to lung inflammation. It was observed that patients with HHV 8-related MCD often presented severe anemia that was associated with autoimmune hemolysis or hemo phagocytic syndrome. Both of these complications remained rare in patients with HHV-8-unrelated MCD (Wu et al., 2017) (Tabata et al., 2019).

Though not completely studied, the Mediterranean region has brought complexity to the clinical diagnosis of Castleman Disease. In the Mediterranean and Japan region, a gene called Mediterranean Fever (MEFV) affects how iMCD manifests with more symptoms including fever and low levels of hemoglobin. This could further imply that environment and ancestry does play a role in the pathogenesis of Castleman Disease (Endo et al., 2021).

Discussion

This paper sets out to explore the links between genetics vs epidemiology and Castleman Disease. Several limitations exist to this paper, one being the small sample size of patients observed due to the rarity of this disease. Another limitation involves the lack of previous research on Castleman Disease. Our conclusion reveals that the cause of Castleman Disease is complex and, in some cases, still largely unknown. As of now, there are no proven environmental causes of Castleman Disease. Unicentric Castleman Disease seems more likely to have its cause

rooted in genetics. As for Multicentric Castleman Disease (MCD), often associated with HIV and HHV-8, there is more evidence that this form is linked to epidemiological factors. However, this correlation is not indicative of causation; there is no proof that HIV or HHV-8 cause MCD. Though there is no solid evidence, there is a lot of speculation in the scientific community that the environment plays a large factor in the manifestation of Castleman Disease. Though perhaps not the sole cause since genetics could play a role, it seems very likely that the environment contributes to the progression of the disease and may very well even be an important cause of Castleman Disease.

We also noticed that, regarding the relationship between environment, MCD, HIV, and HHV-8, MCD pathogenesis is more related to its association with HIV and HHV-8 rather than direct environmental factors. Rather than being a direct catalyst to MCD development, the epidemiology plays an indirect role in MCD pathogenesis via HIV and HHV-8. Because the epidemiology plays a more prominent role in HIV and HHV-8 development, by proxy this also affects the probability of MCD development. While this is not a testament of whether our hypothesis is correct or not, it provides interesting insight into the nuances of the topic that were previously not understood.

There is also an interesting link between genetics and the environment. Genetic mutations are acquired throughout one's lifetime and often affected by environmental factors. Thus, since genetics and the environment are already so interwoven, it is likely that a combination of genetics and environment play a role in the development of Castleman Disease, both its Unicentric and Multicentric forms.

Further research is necessary to understand some of the complexities of Castleman Disease in relation to regional genetics. In particular, location specific genes, such as the MEFV

found in the Mediterranean and Japanese regions, could be a point of examination for correlation of regions that are more susceptible to Castleman Disease. Moreover, there can be a possibility some regions have worse symptoms or are less likely to have Castleman Disease due to their genetic makeup. Taking this a step further, it may be possible to use gene editing such as CRISPR to eliminate such genes that are affecting the expression of Castleman Disease to hopefully improve the condition of patients.

Conclusion

As discussed in the results, there is no decisive conclusion as to the cause of Castleman Disease though there are a few genetic aspects that have been uncovered. We analyzed literature regarding Castleman as a disease, its genetics and epidemiology, as well as its relationship to HIV and HHV-8. One correlation regards genetic mutations that are acquired through horizontal transmission seen in patients with Castleman Disease. Moreover, HIV and HHV-8 are both likely related to the causes of Multicentric Castleman Disease due to the high number of individuals who have these viruses that then acquire CD. Little research has been done on Castleman Disease, in the U.S. and globally. Furthermore, the examination this paper conducted on Multicentric Castleman Disease remains limited due to few publications on Castleman Disease. These limitations are due to the relatively small population size of patients to study and observe. However, through further research on genetics and epidemiology globally, Castleman Disease and its enigmas can be solved or at least well understood. The purpose is to increase the efficacy of current and future treatments to improve patients' livelihoods.

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