University of Nevada, Reno

Huntington's Disease: N17 Domain and Its Role in Disease Pathogenesis and a Clinical Case Study

A thesis submitted in partial fulfillment

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by

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ABSTRACT

Huntington's disease (HD) is a hereditary neurodegenerative disease that results in a progressive decrease in mobility and accompanied by emotional disturbance. Even though the location of the gene, HTT, which is responsible for the disease has been identified, more questions regarding its mechanism are still unanswered. This leads to a lack of an effective treatment for this disease. Chapter 1 describes HD more closely with detailed discussion of its clinical symptoms and pathogenesis along with current methods of diagnosis and possible treatments that are being investigated. The current and future direction of research in this disease are also addressed. One of these directions is examined in Chapter 2, which is a literature review on the research surrounding the role of the N17 domain in the pathogenesis of Huntington's disease. Finally, a clinical case study is presented to explain the diagnosis and treatment plan for a patient with Huntington's disease.

Acknowledgements

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CHAPTER 1

A Review of the Clinical Features and Pathogenesis of Huntington's Disease

ABSTRACT

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that affects an individual's mobility and emotions. Its clinical features, symptoms, genetic basis, diagnosis, and possible treatments are described here. Because an effective treatment is still lacking, future areas in research are also examined.

INTRODUCTION

Clinical Features and Symptoms

Huntington's disease (HD) is a neurodegenerative disease that affects 5 to 10 individuals in every 100,000 people. However, research have shown abnormally high rate of occurrence in certain regions of the world**.** For example, Huntington's disease is diagnosed in 700 per 100,000 individuals in the region surrounding Lake Maracaibo in Venezuela (Gusella et al., 1993). This disease is named after George Huntington, who first discovered it in 1872 in a population within East Hampton, Long Island. In his publication, Huntington was able to describe the hereditary nature of the disease before the genetic findings by Mendel.

One of the major clinical features that helped Huntington in the discovery of the disease was chorea. Also known as Huntington's chorea, it is defined as a set of involuntary, irregular motor movements. Other physical symptoms include abnormal gait

and dystonia, which describes involuntary muscle contractions. In addition, Huntington's disease can result in a loss of intellectual abilities, such as difficulty in learning new tasks, remembering past experiences, dementia, and making decisions. Emotionally, mood swings, personality changes, and depression are also commonly found in individuals with Huntington's disease. All symptoms associated with this disease tend to arise during the middle age and will continue to worsen for 10 to 30 years prior to death.

The course of the disease can be broken down into three main states (Pidgeon & Rickards, 2013). At the early stage, symptoms are mild and may not disrupt the daily life of the individual. Patients can still be working despite the rare occurrences of involuntary movements. During the middle stage, the quality of life began to decrease and patients often need assistance with their daily activities. Chorea appears more frequently while difficulty swallowing and dementia becomes more prominent. Lastly, at the late stage, patients will require complete care from others. Thus, some will enter into nursing homes or other long-term care facility. Ability to move or verbally communicate is gone in these patients. The set of involuntary movements is replaced with rigidness in body. At the end, the cause of death is often related to pneumonia or heart failure.

Treatment

Ever since the initial discovery of the disease, researchers have worked on different possible drugs for its treatment. However, an effective cure has not yet been found. Most pharmacotherapy utilized today focuses on treating the symptoms of the disease by restoring the balance of neurotransmitters within the body, such as GABA,

dopamine (DA), and glutamate (Pidgeon & Rickards, 2013). Side effects of fatigue and hyperexcitability have been noted for these drugs. The current pharmacotherapy for Huntington can be divided into two major categories. Drugs for the treatment of motor symptoms include dopamine depleting agents (tetrabenazine, TBZ), DAD_2 receptor antagonists (typical and atypical neuroleptics), GABA-agonists, and anti-glutamatergic agents. Drugs for behavioral and cognitive symptoms include antidepressants (selective serotonin reuptake inhibitors, SSRI), acetylcholinesterase inhibitors for memory, and neuroleptics.

A detailed set of clinical studies has been conducted on the effectiveness of these pharmacotherapy. In the study for the class of DA depleting agents, TBZ treatment was compared to a placebo group. It was found that patients treated with TBZ experienced a decline of 5 units of chorea severity compared to 1.5 units in the placebo group. However, this effectiveness was not found in the other groups of drugs. The study on neuroleptics, including Clozapine, Tiapride, and Pridopidine, showed little benefits from these treatments. Some of the patients experienced similar effects as placebo while others have adverse side effects. Lastly, the study on drugs for cognitive symptoms, including antidepressants, also show no significant positive effects. The researchers concluded that there is the greatest evidence supporting the benefits of tetrabenazine (TBZ) in improving motor symptoms. However, they also noted the inconsistency in treatment results and the difficulty in measuring changes in cognitive symptoms, such as mood and personality.

Genetics

The genetic cause of Huntington's disease was first discovered by scientists in 1994. It is an autosomal dominant disease caused by a mutation in the huntingtin (HTT) gene on chromosome 4 (Bates, 2005). CAG nucleotide repeat within exon 1 of HTT gene leads to elongation of polyglutamine tract at the amino terminus of the HTT protein which results in protein aggregation. Normal individuals have between 16 to 20 CAG repeats while affected individuals have over 35 CAG repeats.

Diagnosis

The diagnosis of this disease requires genetic test and the study of the patient's medical history. The genetic test is usually done with a sample of blood, hair, or other tissue, and it will confirm the presence of the mutated gene for the HTT protein. This test is often recommended to patients with suspected symptoms or those who are at risk due to parent's history.

CONCLUSION

For a long period of time, most research for Huntington's disease were dedicated to locating the gene that is responsible. After the groundbreaking identification, scientists are now focused on how the mutation causes the disease using different molecular approach and experiments on model organisms, commonly mice. As discussed above, the current treatment plan for the disease is not very effective and prognosis is not hopeful.

More resources have been allocated toward clinical research with the goal of understanding how symptoms progress over the course of the disease. Furthermore, a variety of neuroimaging techniques and have been utilized to investigate the effects of the disease on physical brain structures. With a greater understanding of the mechanism of the disease at both the genotypic and phenotypic level, the hope of finding a cure for Huntington's disease can become a reality.

CHAPTER 2

N17 Domain and Its Role in the Pathogenesis of Huntington's Disease

ABSTRACT

Ever since the identification of the gene responsible for Huntington's disease, it has been a goal to provide a detail explanation of how this gene and its corresponding protein affects the development of the disease. The molecular focus of the following study is on the N17 domain of the huntingtin gene. A transgenic mouse model with the N17 mutation was created for the conduction of these experiments. Through observations of phenotypic behaviors, such as chorea movements, and immunostaining for protein accumulation, it is apparent that the N17 domain plays a role in the onset and severity of Huntington's disease symptoms. With the results from the study, a possible model of mHTT nuclear pathogenesis has been proposed. Even though it is a preliminary model, future evidence can lead to a greater understanding of the underlying mechanism behind the causes of Huntington's disease and the its relationship with the N17 domain.

INTRODUCTION

Huntington's disease is a rare neurodegenerative disease that is often diagnosed during the middle age. Because of the lack of an effective cure and treatment plan, the prognosis after diagnosis is not hopeful. Most patients die from other related secondary causes, such as pneumonia and heart failure, after about twenty years. The genetic cause of this disease has been identified as a mutation at the huntingtin (HTT) gene. It is characteristic for the mutant huntingtin (mHTT) to accumulate in the cytosol and nucleus of the cell. This accumulation leads to brain atrophy, a loss of striatal medium spiny neurons (MSNs), and loss of cortical pyramidal neurons (CPNs) (Gu et al., 2015). MSNs are comprised of most of the neurons in the basal ganglia, and they play a special role in the GABA-ergic inhibitory action. Cortical pyramidal neurons are also important in relying excitation signals. In addition, neurodegeneration in Huntington's is often accompanied with neuroinflammation which is an important phenotypic indicator throughout the study (Maiuri et al., 2013). One of the main molecular focus of this study is on the N17 domain of the huntingtin gene. The N17 refers to the first 17 amino acid at the N-terminal of the gene. It is located directly upstream of the polyglutamine (polyQ) domain. The N17 segment assists in the formation of oligomers, influences the aggregation of mHTT-exon1 fragments, and affects the nucleocytoplasmic trafficking of mHTT (Gu et al., 2015). These roles lead to the question of rather or not mHTT aggregation can be suppressed with manipulation of the N17 domain. Possibilities include the deletion of N17 or overexpression of its binding protein Tcp1. N17 has been proven to be a key regulatory component for the HTT gene with important posttranslational modifications, such as phosphorylation, ubiquitination, and acetylation.

Specifically, the phosphorylation of serines 13 and 16 was shown to reduce oligomerization and aggregation of mHTT fragments. With these information, the researchers created Bacterial Artificial Chromosome (BAC) transgenic mouse models that express the human mutant (97Q) or wild-type (31Q) HTT gene with the deletion of residues 2 to16 in N17 domain. Throughout this study, these mice were used to gain a better understanding of the importance of the N17 domain in affecting mHTT-induced disease pathogenesis of Huntington's disease.

METHODS

The study began by first creating transgenic model mice with ΔN17, deleted residues 2 to 16, form of human Huntington's disease. After confirming the specific deletion in the model mice, engineered human genomic BAC previously used for other BACHD mouse models were used to express ΔN17 forms of mice. This resulted in two types of mice: mutant denoted as ΔN17-mHTT-97Q and wild type HTT denoted as ΔN17-HTT-31Q. Then, these BACs were injected into inbred FvB/N embryos to get transgenic mouse lines (N, L, and A lines) all with ΔN17 forms of mHTT. In addition to the transgenic lines, a control line was created with ΔN17-HTT-31Q noted as BAC-WT-ΔN17. Most of the experiments conducted in this study focused on the BACHD-ΔN17-N line, thereafter referred to as BACHD-ΔN17.

The first experiment conducted was to find out if N17 is required for the function of huntingtin during the development of the mice. It was hypothesized that mice with full length mHTT or mHTT with N17 mutations can reverse the adverse phenotypes in *Htt* null mice. In order to answer this question, the researchers crossed BACHD-ΔN17 or

BAC-WT-ΔN17 onto mice Htt null background. This cross resulted in mice that were phenotypically no different than wild-type up to 2 month old. Next, the researchers wanted to investigate if BACHD-ΔN17 mice show the same motor and behavioral deficits as those commonly associated with Huntington's disease. BACHD-ΔN17 and wild-type mice up to 11 month old were compared on the basis of their motor function and behavior under different environment. They started by comparing body weight of transgenic mice to wild-type at 2, 6, and 11 month old. Interestingly, both gender of transgenic mice were heavier than their wild-type counterpart at 2 and 6 month old. However, this difference drastically increase at 11 month. Then, the BACHD-ΔN17 mice were placed on an accelerating rotarod to measure motor coordination. Spontaneous locomotion and gait was tested with the open field test and the forced swim test (Figure 1).

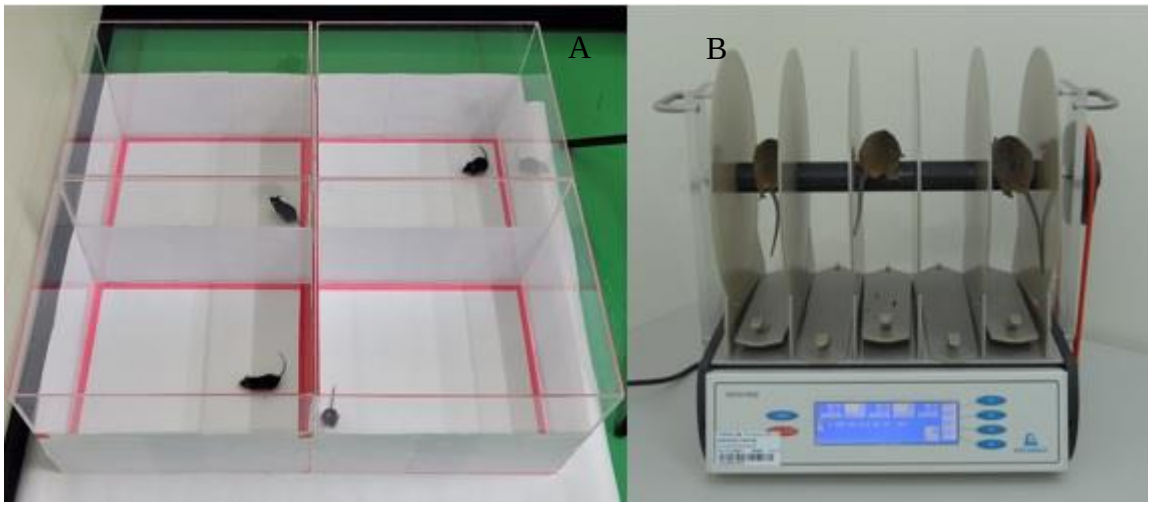

Figure 1. Behavioral and Motor Test Set-Up. A. Open field test. B. Accelerating rotarod.

Abnormal and uncontrolled movements are characteristic symptoms found in Huntington patient, and they are termed Chorea/Dystonia-Like (CDL) movement in this study on mice. Both BACHD-ΔN17 and wild-type mice were observed and measured at different age for CDL movement. To accompany the study on the movement deficits of these transgenic mice, local field potential recordings were taken in the cortex and dorsal striatum of the mouse brain to measure gamma wave activity.

Gliosis refers to the change of glial cells in response to damage to the Central Nervous System, specifically proliferation and hypertrophy of astrocytes, microglia, and oligodendrocytes (Gusella et al., 1993). In order to analyze gliosis and atrophy, brain slices from 2 and 10 month old BACHD-ΔN17 and wild-type mice were examined. Also, a three-dimensional interpretation of these brain slices known as stereology was performed. A key molecular indicator of Huntington's disease pathology is the presence of aggregated mHTT polyQ fragments in the cell nucleus and cytoplasm. Through the usage of human mHTT-exon1 specific antibodies that are sensitive to aggregated mHTT, aggregates can be detected in the brain slices of different age group of transgenic mice.

RESULTS

The various experiments that were conducted on the BACHD-ΔN17 and wild-type mice led to some interesting findings that help bridge the relationship between N17 domain and the pathogenesis of Huntington's disease. First, it was found that the N17 domain is not needed for the proper functioning of Htt during a mouse embryonic development (Gu et al., 2015). Therefore, the N17 deletion mutation does not affect the function of the gene in vivo. Next, the comparison of weight loss between BACHD-

ΔN17 and wild-type mice indicated a significant decline in weight in 10 and 11 month old BACHD-ΔN17 mice. This loss is not observed in the wild-type. The significance of the age of the mice appears again in the result of the accelerating rotarod test. At one month of age, both group of mice show normal performance on the rotarod. However, a decline in performance began to emerge around 6 month. While BACHD mice can still run on the rotarod at 12 month, BACHD-ΔN17 mice's ability is completely compromised by the eighth month. Similarly, BACHD-ΔN17 mice showed significant difficulty in locomotion and gait during the open field test at about 8 month old. In addition, BACHD-ΔN17 mice had more frequent falls than wild-type at 10 month old.

BACHD-ΔN17 mice further demonstrated abnormal Chorea/Dystonia-Like (CDL) movements. These movements included frequent side-to-side swinging of the head and upper body and retroflex of the head and neck that lasted a few seconds. These were noted in 11 month old BACHD-ΔN17 mice but not in the wild-type. It was also discovered that these CDL movements have age dependent onset and is progressive as the animal gets older. For some BACHD-ΔN17 mice, these abnormal behavior begin at 7 month and increase in frequency by ten-fold for the next three months. The recording of gamma activity within the cortex and striatum of BACHD-ΔN17 mice also resulted in interesting findings. BACHD-ΔN17 mice showed short duration (100 to 200 ms), large-amplitude activity within the low gamma range, which is between 25 and 55 Hz. On the other hand, wild-type mice only revealed minor gamma activity. It was concluded that these abnormal striatal gamma frequency is associated with CDL movements observed in BACHD-ΔN17 mice.

After evaluating the brain slices of the transgenic mice, it was noticed that BACHD-ΔN17 mice experience significant forebrain weight loss between 6 and 10 month of age. Specifically, they have 34% less forebrain weight than 10 month old wild-type. However, this atrophy seems to be selective to just the cortex and striatum because the cerebellum appeared to have only minor weight loss at the same time period. The selectivity is even more apparent through three-dimensional stereology. This method allowed for the counting of immunoreactive MSNs within the stratum. It was found that BACHD-ΔN17 mice have lost 40% of striatal MSNs by 10 month.

By using specific antibodies, the presence of aggregated mHTT polyQ fragments were clearly seen. In 2 months old mice brain slices, no aggregates were detected. At 4 months old, BACHD-ΔN17 brain slices showed mHTT nuclear staining along with small nuclear inclusions in cortex but none in striatum. Finally, at 6 months and older, both diffuse nuclear staining and nuclear inclusions were found in the cortex and striatum of BACHD-ΔN17 brain slices (Figure 2).

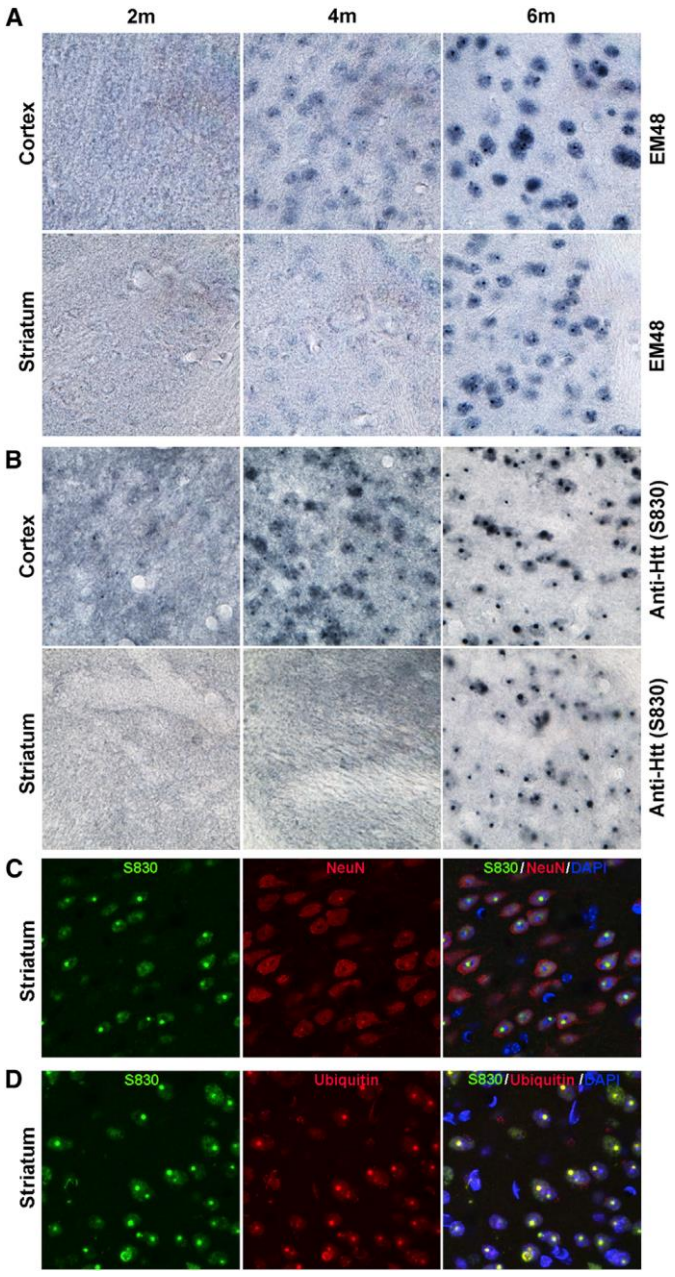

Figure 2. mHTT Nuclear Accumulation and Aggregation in BACHD-ΔN17 Mouse Brains. A. Immunostaining with EM48 antibody. B. Immunostaining with S830 antibody.

DISCUSSION

The objective of the series of experiments conducted was to use a transgenic mice model with either mutant or wild-type HTT lacking the N17 domain to understand the effect of N17 on mHTT nuclear aggregation and phenotypic pathogenesis. This resulted in various findings. First, it was apparent that BACHD-ΔN17 mice showed earlier onset and more severe disease symptoms than their wild-type counterpart. These symptoms include movement deficiency and chorea-like behaviors. The study also indicated that the N17 domain is not required in the functioning of HTT during mouse development. BAC with mutant or wild-type HTT lacking N17 domain can actually reverse the lethal phenotype of Htt null mice. In addition, it was found that BACHD-ΔN17 mice shows

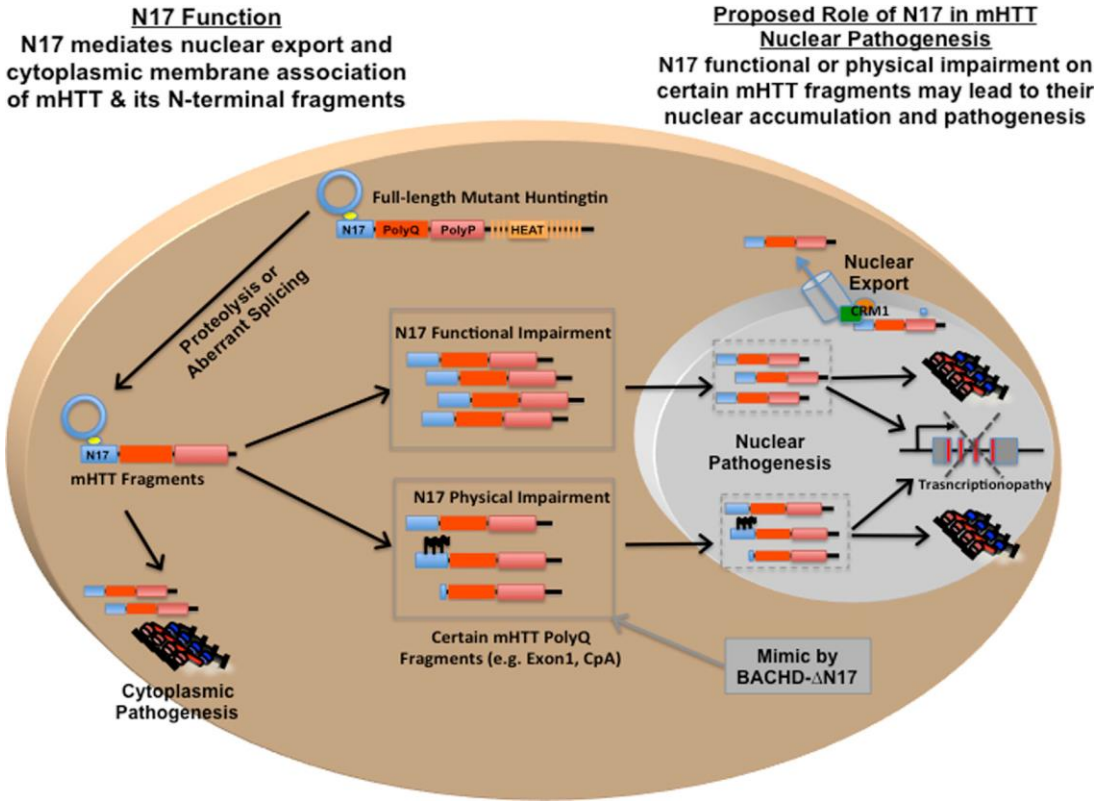

Figure 3. Proposed Model of N17 Domain Role in Regulating Nuclear Pathogenesis in Huntington's Disease.

significant increase in mHTT aggregation, particularly nuclear mHTT aggregates. These findings supported the initial hypothesis that the N17 domain plays a role in regulating the pathogenesis of Huntington's disease. To further this discussion, the researchers proposed a model of how N17 can carry out this role (Figure 3). They believe that two main events are needed in order for nuclear pathogenesis to occur. First, the generation of small mHTT fragments is required. These fragments would be protected from nuclear translocation or accumulation by N17 domain. Second, the N17 role in nuclear export and cytoplasmic membrane association of the mHTT fragments must be impaired. This would lead to nuclear aggregation and pathogenesis within the cell. The researchers have also proposed a few approach to the future direction of this field of study. First, it is important to acknowledge the limitation of the current study due to the use of a transfected non-neuronal cell line. Future studies should expand the current observations into primary neuronal cells. Secondly, the aforementioned model also requires the support of further testing. It should include proteomic analyses of accumulating mHTT within the nuclei of Huntington's disease patients or comparable mouse models.

Chapter 3

Huntington's Disease: A Clinical Case Study

Introduction

This is a case regarding a 45 year old white male, Chris, who visited his physician's office with complaints of minor involuntary muscle contractions and body rigidness which led to difficulty with certain physical activity. The background of this patient will be further investigate to better understand these symptoms and identify the possible source of the problem.

Chris Harrison

Chief Complaint

"For the past few months, I have been having weird contractions and stiffness in my muscles."

History of Present Illness

Chris mentioned that his symptoms first appeared about six months ago. At that time, he was a soccer coach for his son's team. During a weekly practice, he suddenly felt weakness in his legs and fell over onto the grounds. This incident did not result in any injuries. At first, he thought it was just muscle spasm from over exertion. He rested and stopped strenuous activities for a week, but the symptoms did not ceased. Over the months, he began to experience more involuntary muscle contractions in his legs and arms. He also described rigidness throughout his body. He mentioned that there is no pain that accompany the symptoms, but these episodes have occurred more frequently in the past four weeks. Additionally, he noticed a sense of imbalance and a feeling of "falling over" when he walks. Chris emphasized how he has always been a physically active

person, so these symptoms have really affected his lifestyle. He has not been able to exercise as much due to these problems. Therefore, he decided to come seek medical attention.

Past Medical History

Chris occasionally takes Ibuprofen for muscular pain. He had a minor tear in his ACL from playing basketball when he was in college. He has recovered from it since then and don't report any major problem with his knee movement. Chris has never smoke and reports having 4-5 drinks a week. He has no known allergies to any medication.

Social and Family History

Chris grew up in Tacoma, Washington, in a single-mother household with a younger sister. Chris moved to Ellensburg, Washington to attend Central Washington University when he was 18. He majored in marketing and management. He moved back and worked in Tacoma after graduation. When he was 30, he relocated to Reno to work for the Atlantis Casino in town. He is still employed there as a senior marketing coordinator. He and his wife have been married for ten years, and they have two sons. During his free time, Chris enjoys outdoor activities and a variety of sports, such as soccer and football. He coached his son's soccer team for 2 years but no longer does.

Chris's mother and sister still live in Tacoma. They are both relatively healthy with no chronic disease. His father passed away in a car accident when Chris was a teenager, and he had no serious medical condition at the time of his passing. Both of Chris's maternal grandparents passed away in their eighties due to complications from

chronic heart disease. His paternal grandfather passed away when he was 70 years old from lung cancer with a long history of smoking. His paternal grandmother was diagnosed with Huntington's disease at 50 years old, and she committed suicide at 55.

Physical Exam

Height: 5'11'' Weight: 170 lbs Blood Pressure: 125/80

Temperature: 98.5 F Pulse: 80 beats/min Respiratory Rate: 19 breaths/min

General:

Appears physically fit and alert. No acute distress. Nervous and agitated.

HEENT

Head:

NCAT. No TMJ tenderness.

Eyes:

Clear conjunctiva. PERRLA.

Ears:

Canals are clear bilaterally. Tympanic membranes are clear bilaterally and have good reflex to light.

Throat and mouth:

Moist mucous membranes. Intact dentition. No oral lesions. No pharyngeal edema or erythema.

Neck:

No tyromegaly and no masses. No LAD. No bruits heard in the carotid arteries. No JVD.

Chest/Lungs:

No W/R/R. Symmetric chest expansion with no deformity.

Heart:

RRR. Normal S1-S2. No m/r/g.

Abdomen:

Flat and soft. Not tender. No mass. No HSM. Muscle spasm noticed during exam but no guarding or rigidity.

Musculoskeletal:

Spine aligned. Well-muscled. Muscle strength is 4/5 in bilateral upper and lower extremities. No joint enlargement or tenderness.

Neurological:

Clear speech with slight irritation to questioning. No facial droop. Abnormal gait with slight foot drop. DTR 3+ B/L in upper extremities. DTR 4+ B/L in lower extremities.

Skin:

Well perfused with good capillary refill. No rashes or lesions.

Diagnostic Work

Complete Blood Count (CBC)

RBC count:	5.0×10^6 / μ	($4.2\text{-}5.9\times10^6$ /μ)
Hemoglobin:	15 g/dL	(14-17 g/dL) male
Hematocrit:	45%	(41%-51%) male
MCV:	85 fL	(80-100 fL)
MCH:	33 g/dL	(32-36 g/dL)
White Cell count:	6,000 / μ	(4,000-10,000/μ)
Platelets:	250,000 / μL	(150,000-350,000/μL)
ESR:	10 mm/h	(0-15 mm/h) male

Basic Metabolic Panel

BUN:	15 mg/dL	(8-20 mg/dL)
Bicarbonate:	25 meq/L	(23-28 meq/L)
Creatinine:	1.0 mg/dL	(0.7-1.3 mg/dL)
Glucose:	86 mg/dL	(70-100 mg/dL)
Chloride:	101 meq/L	(98-106 meq/L)
Calcium:	9.2 mg/dL	(8.5-10.2 mg/dL)

Potassium:	4.2 meq/L	(3.5-5.0 meq/L)
Sodium:	142 meq/L	(136-145 meq/L)

Genetic Test

No. of CAG Repeats	50 repeats	(≤28 repeats)

Impression: Positive for Huntington's disease

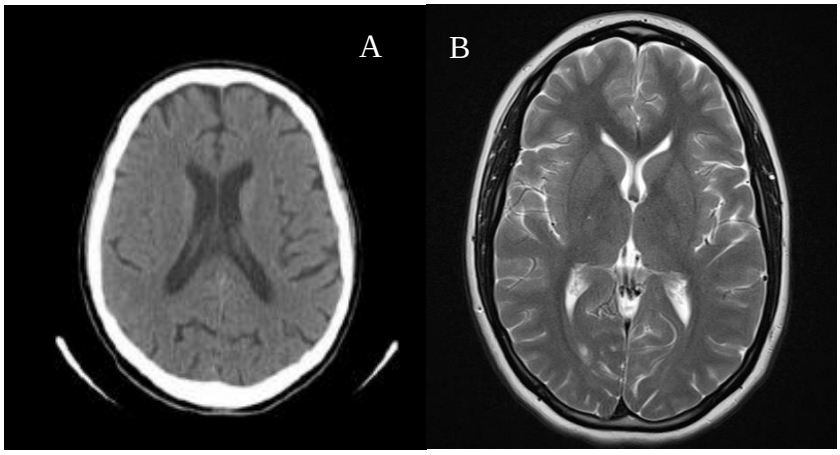

Figure 4. Images from A. computerized tomography (CT) and B. magnetic resonance imaging (MRI) head scan of the patient.

The initial blood tests indicate no abnormality. Due to the patient's family history and current presence of symptoms, a genetic test was ordered. The result shows a high count of CAG repeats greatly above the normal range. This further points to a diagnosis of Huntington's disease.

Differential Diagnosis

Different musculoskeletal related diagnosis were considered in accordance to Chris's symptoms. First, muscle strain was a possibility due to the amount of physical activity that he is involved in. However, the duration of the persisting symptoms make overexertion an unlikely explanation. Another possible cause of the symptoms is tendinitis, which is often associated with repeated activities or a sudden injury that leads to inflammation. Chris's job does not require activities of such repeated impact, and he has not reported any recent physical injury. Therefore, tendinitis can be ruled out. Electrolytes imbalance was also ruled out due to the normal values on the metabolic panel. With the symptoms of muscle spasm, the possibility of a stroke or a tumor was considered. However, Chris's healthy lifestyle and the normal CT head scan (Figure 1) make this option unlikely. After further questioning, Chris reported a decrease in memory and getting easily irritated in recent months. He did not mentioned them at first because he initially thought these issues were his emotional reaction to the inconvenience of his physical symptoms. However, it is more likely that his emotional disturbance is contributed to a cause other than a physical one. Therefore, Creutzfeldt-Jakob disease (CJD) was considered despite its rare occurrences. This was ruled out because of its later onset of symptoms at about age 60. In addition, the MRI scan shows no brain degeneration that is characteristic of CJD. Chris's family medical history makes it necessary to order a genetic test for the possibility of Huntington's disease.

Diagnosing

Huntington's disease is an autosomal dominant genetic disorder. Chris reported that the disease has appeared in his family. His paternal grandmother passed away a few years after being diagnosed with it. Because Chris's father passed away from an accident before the common age of appearance for Huntington's symptoms, it is unclear if he had the genetic mutation. However, it is highly possible that Chris has unknowingly inherited such faulty mutation from his father.

The symptoms of Huntington's disease commonly appear during middle age, between 40 and 50 years old, which places Chris in this range. At an early stage of the disease, symptoms include irregular motor movements (chorea), involuntary muscle contractions (dystonia), and mood swings with prominently depressive episodes. Chris has experienced all these problems in the past few months. In addition, the genetic test result indicates that he has an abnormally high number of CAG repeats which is a definitive characteristic seen in patients with Huntington's disease. While normal individuals have between 16 to 20 CAG repeats, affected individuals can have over 35 repeats. According to the test, Chris has 50 repeats in his HTT gene. Along with the symptoms, this test further confirms the diagnosis of Huntington's disease.

Treatment

In order to reduce the symptoms of Huntington's disease, the patient is prescribed with Tetrabenazine and antidepressant. Tetrabenazine has been proven effective against chorea. It is recommended that the patient begin with the lowest dosage once a day to observe for any abnormal side effects. Depending on the patient's response to the

medication, Tetrabenazine can be slowly increased to three times a day. Antidepressant is prescribed to target the depressive episodes that accompany the disease, especially since there is a history of suicide in Chris's family. The patient is referred to a neurologist to manage the course of progression of the disease, and a psychologist was recommended to help with the psychological symptoms. In addition to medications, regular exercise is also part of the treatment plan. It has been shown that proper exercise can help with some of the physical symptoms of the disease. After the initial establishment of the treatment plan, Chris will be seeing his neurologist every few months to determine if any adjustment is needed.

Prognosis and Plan Implementation

It was explained to Chris that there is currently no cure to Huntington's disease. Most patients can take medications to control symptoms. However, the overall mobility of the patient will slowly decrease while he becomes more dependent on others for daily life functions. In the later stages of the disease, Chris can become wheelchair-bound. With proper medications and a positive mindset, many patients with Huntington's disease have a prognosis of 15 to 25 years. It is recommended that Chris schedule an appointment for every three to six months to monitor the progression of the disease and further plans can be implemented according to his symptoms. Huntington's disease is a very serious diagnosis, and it can have a strong emotional toll on the patient and his family. Chris has been referred a local Huntington's disease support group in Reno to receive psychological support and resources through the course of the disease.

This diagnosis is expected to have a strong effect on the life of Chris and his family. A treatment plan and other resources have been discussed with them. Chris's current job does not require a lot of physical activity, so it was suggested that he can continue to work until his symptoms prevent him from doing so. By maintaining his current social interactions and going to the recommended support group, Chris will receive emotional support as he experience through the disease. A positive mindset will assist proper implementation of the treatment plan.

Aside from helping Chris accept this diagnosis, it is also necessary to educate his family members of its impact. Attending individual and group therapy sessions through the support group is highly recommended for Chris and his immediate family members to allow them to receive assistance in handling this diagnosis. Because Huntington's disease is an autosomal dominant genetic disorder, it is an option for Chris's two sons to receive the genetic test to look for the presence of the affected gene. A referral to a geneticist can be provided if needed, but the decision to obtain a genetic test is highly controversial. Some families choose to not undergo the genetic test while others allow the children to make the decision for themselves when they are older. Regardless, this requires serious consideration so Chris and his wife were asked to discuss and to determine if they want their children tested.

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