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A REVIEW ON HAJDU-CHENEY SYNDROME (HCS)

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Abstract : This study has been undertaken to investigate the determinants of stock returns in Karachi Stock Exchange (KSE) using two assets pricing models the classical Capital Asset Pricing Model and Arbitrage Pricing Theory model. To test the CAPM market return is used and macroeconomic variables are used to test the APT. The macroeconomic variables include inflation, oil prices, interest rate and exchange rate. For the very purpose monthly time series data has been arranged from Jan 2010 to Dec 2014. The analytical framework contains.

Keywords: Hajdu-Cheney Syndrome, NOTCH2, dental anomalies, skeletal abnormalities.

INTRODUCTION

Hajdu-Cheney syndrome, or HCS, is an uncommon genetic disorder that is inherited autosomally, however it can also manifest sporadically. Acroosteolysis of the distal phalanges, severe osteoporosis with fractures, anomalies of the craniofacial and dental regions, and small stature are its defining features. Prominent skeletal characteristics in patients with HCS include dental anomalies, micrognathia, mid-face flatness, and facial dysmorphisms. This disorder affects less than one person per million (<1/1,000,000) and is brought on by a heterozygotic mutation in the NOTCH2 gene, which is found on chromosome 1p13–p11. HCS is inherited autosomally dominantly, while there are reports of individuals with random mutations.[1]

N. Hajdu published the initial description of the illness in 1948, and D. Cheney finished it in 1965. Since then, about 50 cases of patients with HCS have been reported. All of these patients generally exhibit generalized osteoporosis and distal phalangeal osteolysis, along with other disorders like skeletal dysmorphia, early tooth loss, craniofacial and skeletal dysmorphia, and short stature.

The highly uncommon genetic condition known as Hajdu-Cheney syndrome (HCS) is caused by a de novo mutation in the NOTCH2 gene, which codes for the notch2 protein. The mutation causes notch2 signaling to be amplified. Transmembrane protein notch plays a key role in tissue formation and aids in the determination of cell destiny in a number of physiological processes. Upon activation of this signaling

pathway, notch2 causes positive regulation of receptor-activated nuclear factor-κB ligand-induced osteoclastogenesis, which leads to bone deformations.Patients with this condition may appear with varying clinical presentations because the heterogeneity in NOTCH2 expression results in phenotypic diversity. Furthermore, a single patient may not fully experience this condition due to its broad and particular clinical range.[2,3]

EPIDEMOLOGY

The frequency of Hajdu-Cheney syndrome is fewer than 1 in 1,000,000 live births. About 50 instances have been reported globally since 1948. Although there have been isolated cases documented, the condition is hereditary and is inherited autosomally dominantly. It may happen to people of different ethnic backgrounds and affect people of both genders. Although de novo mutations are sometimes possible, autosomal dominant inheritance is the usual pattern for HCS inheritance. The illness frequently appears in childhood or early adulthood, although diagnosis can be difficult due to its inconsistent clinical presentation and low frequency.[4]

ETIOPATHOGENISIS

A heterozygotic mutation of NOTCH2 is the source of the hereditary illness known as HCS. Because the NOTCH signaling system is made up of several interconnected events that are directly related to both homeostasis and skeletal development, changes to this route result in problems with both processes.

Transmembrane proteins called NOTCH receptors are divided into three main sections: an extracellular domain that contains multiple EGF (epidermal growth factor)-like repeats; an additional intermembrane domain; and an intracellular domain that includes nuclear localization signals, multiple ankyrin repeats, and a proline-, glutamic acid-, serine-, and threonine-rich domain called the PEST domain, which is involved in protein recycling. Five ligands (JAG1, JAG2, and DLL 1, 2, and 4) and four receptors (NOTCH 1, 2, 3, and 4) make up NOTCH.

When a cell's ligand attaches to its receptor, the intracellular domain separates and moves to the cell nucleus to start fulfilling its role. This initiates the NOTCH signaling pathway. A truncation in NOTCH2's exon 34 in HCS results in a protein product lacking the PEST domain, which elevates NOTCH signaling activity in several tissues and modifies the normal process. The illness results from this, which has a discernible effect on skeletal development and homeostasis.[5,6,7]

SYMPTOMS

Individuals affected by Hajdu-Cheney syndrome may exhibit a wide range of signs and symptoms. Although the disease is congenital—present from birth—some people may exhibit more overt signs and symptoms throughout their teens and early adult years.

Despite being able to identify a distinct syndrome with defining or "core" symptoms, experts still lack a thorough understanding of the condition. A variety of obstacles, such as the limited number of instances that have been found, the dearth of extensive clinical research, and the potential for other genes to impact the condition, hinder medical professionals from gaining a comprehensive understanding of the disorder's symptoms and prognosis. It is crucial to remember that not everyone who is impacted may experience every symptom covered here.

The disintegration of bone and tissue (osteolysis), especially in the outermost bones of the fingers and toes (acroosteolysis), is a distinctive observation. This might be mild, or it could involve swelling, discomfort, inflammation, and strange feelings like tingling or burning (paresthesia). Patients with severe symptoms may have shortened, rounded, or clubbed fingers and toes. In most cases, the fingers are more severely impacted than the toes.[8,9]

The most typical clinical signs of HCS are the following ones:

1. **Skeletal Disturbances**:

   • Short stature: People who have HCS frequently have lower-than-average heights.

   • Craniofacial anomalies: These can be dental abnormalities including crowding, malocclusion, and early tooth loss, as well as features like a tiny chin, wide-set eyes, and a prominent forehead.

   • Spinal abnormalities: In HCS, kyphosis (an extreme outward curvature of the spine) and scoliosis (a sideways curvature of the spine) are prevalent.

   • Hypermobility of the joints: Extreme joint range of motion can result in enhanced flexibility but also in the possibility of joint instability and discomfort.

2. **Problems with the Bones**

• Osteoporosis: People with high calcium syndrome (HCS) may have low bone density, which increases their risk of fractures.

• Wormian bones: There may be additional bones inside the cranial sutures.

3. **Abnormalities of Connective Tissue**:

• Abnormalities of skin: Excessive folds and skin laxity, especially on the hands and feet, may be seen.

• Hernias: When internal organs protrude via weak spots in the abdominal wall, it is a result of connective tissue weakness.

• Joint laxity: Excessive lubrication of tendons and ligaments can lead to hypermobility in joints.

4. **Other Features**:

- Abnormalities in Cardiovascular system: Although less often, cardiac problems or anomalies in blood artery structure might occur in certain individuals with HCS.
- Abnormalities in Renal system: Some cases of HCS have been linked to kidney abnormalities, including cysts or deformities.
- Neurological symptoms: Rarely, people with HCS may encounter neurological problems including seizures, intellectual incapacity, or developmental delay.

It's crucial to remember that, even among members of the same family, people with HCS can differ greatly in the severity and mix of their symptoms. Furthermore, over time, new symptoms or problems might appear, necessitating constant observation and treatment from medical specialists.[10,11]

Craniofacial features	Skeletal features	Other features
• Facial dysmorphism, micrognathism	• Acroosteolysis, fibular deformities, fractures, joint hyperlaxity	• Short stature, developmental delay
• Open sutures, wormian bones	• Short and broad digits	• Polycystic kidneys
• Platybasia and basilar invagination	• Osteoporosis with fractures	• Neurologic symptoms, hearing loss
• Periodontal disease, tooth abnormalities and loss	• Vertebral deformities, scoliosis	• Congenital heart/vessel defect

Figure 1 : Hajdu-Cheney syndrome Clinical features

DIAGNOSIS

Obtaining a definitive and timely diagnosis of HCS is challenging. Research like Schawo's show that while radiological tests and physical appearance will direct the diagnosis process, genetic testing is required for ultimate confirmation. According to Kawamura et al., magnetic resonance imaging should be done in addition to a physical examination.

A diagnostic algorithm developed by Brennan and Pauli determines the inclusion criteria for this disease based on a number of physiological measures and genetic inheritance derived from the London Dysmorphology Database. Focusing on a range of clinical manifestations, including acroosteolysis, wormian bones or open sutures, platybasia, micrognatia, premature denture loss, coarse face, coarse hair, midfacial flattening, short stature (<5%), and a positive family history, this tool aids in the diagnosis of HCS. Its age-dependent progression and phenotypic alterations establish disparities between adults and children.

Three possibilities are suggested for adults that might result in a positive diagnosis:

• Acrósteolysis with three clinical signs, excluding a positive family history that has been established.

• Acrósteolysis combined with a confirmed favorable family history.

• A verified favorable family history in addition to two other symptoms, excluding acroosteolysis.

Two options are suggested for kids:

• Two symptoms plus a recorded positive family history;

• Four clinical manifestations, excluding a proven positive family history.[12,13]

Hajdu-Cheney Syndrome (HCS) is diagnosed by combining imaging investigations, genetic testing, and clinical assessment. This is a synopsis of the diagnostic procedure:

1. **Clinical Assessments:** A medical practitioner, usually a clinical geneticist or an expert in skeletal dysplasias, conducts a comprehensive clinical examination. A thorough medical history, a physical exam, and an assessment of the symptoms that are now present are all part of the evaluation.

2. **Radiology**: To evaluate the skeletal anomalies typical of HCS, imaging investigations such X-rays, CT, or MRI scans are crucial. Short height, craniofacial anomalies (such as abnormalities of the skull or face), spinal abnormalities (such as kyphosis or scoliosis), and abnormalities of bone density (such as osteoporosis) are a few examples of these findings.

3. **Laboratory testing:** Serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels are among the indicators of bone turnover that may be assessed by blood testing. These examinations can be used to evaluate bone metabolism and spot any side effects like osteoporosis.

4. **Gene Testing:** The most reliable method for verifying an HCS diagnosis is genetic testing. The NOTCH2 gene is sequenced in order to find mutations or variations connected to the condition. Genetic testing can be helpful in confirming the diagnosis, separating HCS from other illnesses that are similar, and yielding important data for genetic counseling.

5. **Differential Diagnosis**: It is crucial to carefully evaluate differential diagnoses due to the rarity of HCS and the overlap of its symptoms with those of other skeletal dysplasias and connective tissue diseases. Based on clinical and laboratory results, conditions such osteogenesis imperfecta, Marfan syndrome, Ehlers-Danlos syndrome, and other uncommon skeletal dysplasias may need to be ruled out.[14,15]

MANAGEMENT

Since there is yet no known cure for Hajdu-Cheney Syndrome (HCS), treatment focuses mostly on controlling the disorder's symptoms and effects. A multidisciplinary approach customized to the individual's unique needs may be used in treatment techniques, which might include the following:

1. **Orthopedic Treatment**: In order to treat skeletal anomalies such joint issues, limb abnormalities, and spinal deformities like kyphosis and scoliosis, orthopedic procedures may be required. Physical therapy, bracing, orthotic devices, or surgical techniques including spinal fusions or corrective osteotomies may be used in this situation. Osteoporosis and other disorders marked by excessive bone turnover are frequently treated with bisphosphonates, a family of drugs that limit bone resorption. Bisphosphonates may be taken into consideration to assist increase bone density and lower the risk of fractures in people with HCS who have osteoporosis or substantial bone loss, even though there is little data specifically related to this condition.[16]

2. **Dental Care**: People with HCS frequently have dental problems, such as malocclusion, overcrowding, and early tooth loss. Regular dental checkups, orthodontic therapy, dental sealants, fluoride treatments, and prosthetic tooth replacements are a few examples of dental management.[17]

3. **Pain Management**: Analgesic drugs, physical therapy, and procedures like spinal cord stimulation or nerve blocks may be necessary for the treatment of chronic pain brought on by skeletal abnormalities or joint issues. Acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs) can be used to treat pain brought on by musculoskeletal complaints, such as joint pain or discomfort from spinal abnormalities.[18]

4. **Bone Health**: Because of aberrant bone remodeling, people with HCS may be more susceptible to osteoporosis. Under the supervision of a healthcare provider, weight-bearing exercise, calcium and vitamin D supplements, and pharmaceutical therapies like bisphosphonates are all possible ways to maximize bone health. Ingesting enough calcium and vitamin D is necessary to keep bones healthy. Calcium and vitamin D supplements may be beneficial for people with HCS, especially if they have low bone density or are at risk of fractures.[19]

5. **Monitoring and Surveillance** To evaluate the course of the disease, spot complications, and take immediate action in the event of an emergency, regular monitoring and surveillance are crucial. Periodic clinical exams, radiographic imaging, laboratory testing, and assessments by a variety of specialists—such as endocrinologists, orthopedists, geneticists, and dentists—may be part of this.[20]

6. **Genetic Counseling**: To inform patients and their families about the hereditary foundation of the illness, the likelihood of a recurrence, and the range of testing alternatives, genetic counseling should be made available to those with HCS. Counseling can assist people in understanding the effects of HCS on themselves and their family members as well as in making educated decisions regarding family planning.

7. **Supportive Care**: It's critical to offer resources and emotional support to people and families impacted by HCS. In order to help people cope with the difficulties of having a rare genetic condition, support groups, patient advocacy organizations, and specialized healthcare experts can provide advice, link people to resources, and create a supportive community.

It's critical that people with HCS collaborate closely with a multidisciplinary healthcare team to create a customized treatment plan that addresses the disorder's physical and psychological components and is suited

to their particular requirements. The results of the reviewed papers on this subject suggest that, despite notable advancements in therapy, a curative treatment for HCS is still lacking.[21,22]

CONCLUSION

To wrap it up, Hajdu-Cheney Syndrome (HCS) is an extremely uncommon genetic illness that manifests as connective tissue manifestations, skeletal deformities, and a variety of systemic characteristics. HCS is extremely rare, but because of its wide range of clinical presentations and possible sequelae, it poses serious issues for afflicted persons and their families. Using the body of research on HCS to guide it, this review has presented a summary of the disorder's pathophysiology, diagnosis, treatment, and clinical aspects.

Individuals afflicted by HCS may exhibit a wide range of clinical presentations, from connective tissue symptoms like skin laxity and joint hypermobility to skeletal deformities including short stature and craniofacial anomalies. Mutations in the NOTCH2 gene, which cause disruption of connective tissue homeostasis and bone remodeling, are the fundamental genetic cause of HCS. A thorough examination that takes into account genetic testing, radiological imaging, clinical judgment, and differential diagnosis is necessary for the diagnosis of HCS.

The main goals of HCS management are supportive care and symptom control, which are achieved by applying a multidisciplinary strategy that is customized to each patient's unique need.

Many elements of HCS remain poorly known despite advancements in clinical care and research, underscoring the need for more study to clarify its underlying pathophysiology, natural history, and best practices in therapy. Research, medical professionals, and patient advocacy organizations must work together to advance understanding, improve diagnosis, and raise the standard of treatment for people with HCS.

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