RUTGERS HEALTH
School of Dental Medicine

Hajdu Cheney Syndrome: Literature Review

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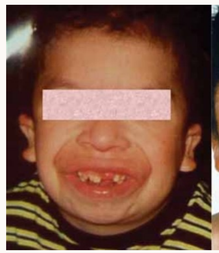
Abstract:
Hajdu Cheney Syndrome (HCS), also known as arthro-dento-osteo dysplasia, is a rare inherited connective tissue disorder characterized by various manifestations including craniofacial anomalies, acro-osteolysis, osteoporosis with fractures, congenital heart defects, hearing impairment, polycystic kidneys, recurrent respiratory tract infections, short stature, and developmental delay. It is an autosomal dominant disorder caused by a mutation in the NOTCH2 gene, with sporadic cases reported. Diagnosis involves genetic sequencing, but initial identification is based on external appearance and radiological findings. Oral features include micrognathia, narrow high palate, dental anomalies, periodontitis, mandibular ramus hypoplasia, early loss of adult teeth, cleft palate, and an abnormal eruption pattern. The disease exhibits phenotypic variability, varies in clinical features, and age-dependent progression. Invasive dental procedures are advised against, as they may pose a risk for medication-related osteonecrosis of the jaw (MRONJ), given the ongoing resorption of the alveolar process.

Background:
Hajdu Cheney Syndrome also known as arthro-dento-osteo dysplasia, Hajdu-Cheney syndrome, acroosteolysis dominant type, Serpentine fibula polycystic kidney syndrome, Orpha number: 955. Originally described by Hajdu in 1948 in a 37-year-old accountant who died 12 years later of severe neurological complications, the syndrome was reported further by Cheney in 1965. Is an extremely rare and heterogeneous disease. HCS follows an autosomal dominant inheritance. but can also result from spontaneous de nova mutation. This disease mainly affects the connective tissue and belongs to the osteolysis syndromes group. Hajdu–Cheney syndrome has a prevalence of less than 1 in 1,000,000 live births Since 1948, The gender or racial differences in HCS prevalence remain unclear.

Etiology:
HCS is caused by a heterozygous mutation in Notch homolog protein 2 gene (NOTCH2) .encodes a transmembrane protein critical in skeletal development and bone remodeling by acting on the cells of osteoclast and osteoblast lineage. The *NOTCH2* mutation is a gain of function, as it results in a longer half-life for NOTCH2 protein. The enhanced NOTCH2 activity promotes osteoclastogenesis and inhibits osteogenesis. The initial diagnosis is established based on the clinical findings (short stature, hand pain, weakness, pathologic fractures, and distal osteolytic lesions) and radiological grounds and is confirmed by molecular detection of pathogenic variants in the *NOTCH2* gene (genetic sequencing). It is mostly diagnosed in adulthood or adolescence with the presence of a positive family history. There has been no link between the severity of disease and age of diagnosis. The clinical manifestation of HCS is highly variable, which makes early diagnosis challenging, resulting in delayed diagnosis in many cases.

Clinical Features:
The disease has three main features: phenotypic variability, a wide spectrum of clinical presentation, and an age-dependent progression. (The clinical phenotype is variable, and none of the patients have all the signs mentioned in the following description). The diagnosis may be delayed until the patient is in the second or even third decade when they typically present with swelling and pain in the fingers. However, Signs of the disease are manifested as early as in the first 2 years of life according to Descartes et al., 2014. The disease has a degenerative nature therefore, the clinical manifestations worsen over time with the onset of many changes from early childhood to late adulthood.



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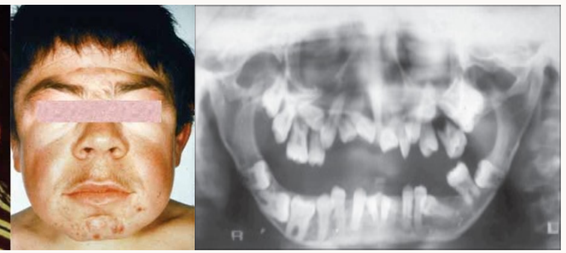

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Common craniofacial and dental features may include:

Optical atrophy, optic disc edema
Hearing loss and Low-set ears
Frontal bossing
Flat nasal bridge
Coarse hair, and a low hairline
Hypertelorism
Bushy eyebrows
Differences in skull shape
open skull sutures
Coarse facial features
Frontal and occipital headaches
long & flat philtrum
Flattening of the midface,
Micrognathia and narrow high palate
Small mouth with dental anomalies
Hypoplasia of ramus of mandible
Early loss of adult teeth
Cleft palate
Underbite or overbite
Thin upper lip
Downturned mouth
Micrognathia,
Premature loss of dentition
Abnormal dental eruptions as well as premature tooth decay and loss.
Hypoplastic maxilla
Malalignment of teeth (severe crowding)
Wide mandibular angle
Periodontitis

Dental management:
Management included identification of the NOTCH2 mutation and treatment with antiresorptive measures. In addition, genetic counseling and antenatal counseling are recommended to explain the risk of inheritance.
To reduce the risk of MRONJ, the following procedures should be performed before the BPs treatment: elimination of infectious foci from oral cavity and correction of fillings and removable prosthetic restorations.
During BPs therapy, patients should be aware of the risk of osteonecrosis of the jaws and the principles of good oral hygiene, and follow-up visits every 3–4 months.
During visits, hygiene, and routine radiological monitoring should be carried out.
If MRONJ occurs and surgical treatment is necessary (extractions, resection of root apices, periodontal surgery), it should be minimally invasive and tissue healing has to be monitored. For example, Extractions should be performed one at a time and the wound should be sutured. Only if the healing after the performed procedure is uneventful may the extraction therapy be continued.
Surgical procedures should be performed in short-term antibiotic therapy. The patient should start taking the antibiotic the day before the surgery and continue the therapy for three consecutive days.
Removable partial denture can be planned but evidence regarding its effect on the progressing alveolar bone resorption is still not clear.
As midface deficiency is another feature in these patients, there is an increased risk of developing skeletal Class III relationship in the future. Even though increased mobility of the teeth, short roots, as well as unpredictable response of alveolar bone to the forces, make the orthodontic treatment more complicated, Bazopoulou-Kyrkanidou et al.10 and Vingerhoedt in 20103 had successfully treated a HCS patient with orthodontic therapy using light force for a long period of time which was well tolerated by the patient.
A new idea in the prevention of MRONJ may be the application of platelet concentrates (APCs). APCs can be effective in regulating healing processes and in angiogenesis triggering.
Alternative therapies may include the following: calcium, vitamin D, vitamin E, ozone, hyperbaric therapy, bio-stimulation laser therapy, preparations of platelet-derived growth factors, platelet-rich plasma and plasma rich in growth factors, and recombinant human bone morphogenetic proteins. Alternative therapy is supportive therapy and cannot be used as monotherapy.

Conclusions:
HCS is characterized by connective tissue disorders, severe bone resorption, and osteoporosis. Its highly variable phenotypes make early diagnosis challenging. the mechanism resulting in HCS is not fully understood, physicians should be aware of variable phenotypes so that early diagnosis and management can be achieved.
Treatment with BP should be done with caution since BPs can alter bone healing and increase the risk of MRONJ.

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