Hajdu-Cheney Syndrome: A case report with review of literature

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ABSTRACT

Hajdu-Cheney syndrome is a very rare connective tissue disorder. It has autosomal dominant inheritance or may occur due to spontaneous de novo mutation. Recent research suggests that it is caused by heterozygous mutation of terminal exon of NOTCH 2. Most characteristic findings include transverse band of acro-osteolysis involving the phalanges of both hands and feet and osteoporosis and deformities involving skull, mandible, spine and other bones. Patient may progressively develop kyphoscoliosis, basilar invagination, and bone fractures due to bone softening. Treatment is symptomatic. In this case report we present clinical and radiological features of a 43-year-old female patient who presented with features of Hajdu-Cheney syndrome.

CASE REPORT

CASE REPORT

A 43-year-old female patient presented to dental outpatient department with history of loose and premature loss of multiple teeth. She was suspected of having hyperparathyroidism and was referred to the endocrinologist in our hospital for further evaluation. She also gave history of pain and progressive shortening of fingers and toes. There was no history of any neurological deficit. On examination the patient was short in stature, had a prominent forehead and mid facial flattening. The fingers and toes of both hands and feet appeared to be short and stubby. There were no signs of local inflammation. Endocrinological and metabolic workup for this patient was normal.

Skeletal survey was performed, which included radiograph of lateral view of skull, orthopentomogram, Waters view for paranasal sinuses, lateral view of dorsolumabar spine, frontal radiographs of hands, feet, pelvis, and chest.

Radiograph of right hand showed transverse band of osteolysis involving distal phalanx of second and third finger and middle phalanx of fifth finger. There was near complete osteolysis of distal phalanx of thumb. Marginal erosion was noted at distal interphalangeal joint of fourth finger (Fig. 1).

Radiograph of left hand showed transverse osteolysis involving distal phalanx of thumb, second and third finger and middle phalanx of fifth finger. The fourth finger was spared (Fig. 1).

Radiograph of right foot showed osteolysis involving distal phalanx of first to fourth toe and middle phalanx of fifth toe (Fig. 2).

Radiograph of left foot showed osteolysis involving the distal phalanges of all toes and periarticular erosion at first metatarsophalangeal joint (Fig. 2).

The soft tissues around the tips of terminal phalanges of both hands and feet appeared normal. No periarticular or any soft tissue calcification was seen in hands and feet.

Lateral radiograph of skull showed multiple wormian bones in the lambdoid suture. There was mild prominence of squamous occipital bone suggestive of bathrocephaly. There was aplasia of frontal sinus and elongated J shaped sella (Fig. 3).

Waters view for paranasal sinuses showed aplastic frontal sinus with markedly hypoplastic maxillary sinuses bilaterally. Unfused metopic suture was also noted (Fig. 4).

Orthopentomogram showed erosion of alveolar margin of maxilla and mandible with loss of multiple upper and lower

teeth. The residual teeth showed loss of lamina dura around them. Dental prosthesis was also noted (Fig. 5).

Lateral radiograph of spine showed osteoporosis of dorsolumbar vertebrae. No osteoporotic compression of vertebrae was seen (Fig. 6).

Frontal radiograph of chest and pelvis showed no obvious abnormality (Fig. 7 & 8).

MRI of brain and spine performed subsequently revealed partially empty sella. No other abnormality was seen in the brain and spinal cord (Fig. 9) .

Based on clinical and radiological features patient was diagnosed as a case of Hajdu-Cheney syndrome. Patient could not afford genetic analysis for NOTCH 2 mutation. Patient is presently on medical line of treatment with vitamin D and bisphosphonates and is advised to come for regular follow up.

DISCUSSION

Hajdu-Cheney syndrome (Synonyms: HCS, acro-dento-osteo-dysplasia, acro-osteolysis dominant type, acro-osteolysis with osteoporosis and changes in skull and mandible or Cheney syndrome), was first described by Hajdu and Kauntze in 1948 as cranioskeletal dysplasia [1, 6]. Cheney brought in another case report in 1965 where he described additional radiological features of the disease including acro-osteolysis [6].

Etiology and Demographics

Hajdu-Cheney syndrome (HCS) is a very rare, heritable disorder of connective tissue with only about 50 cases reported in literature [2]. Recently it has been shown that restricted range of mutations in the terminal exon of NOTCH 2 causes this syndrome [3]. Notch signalling is important in the early skeletal development as well as for the differentiation and function of osteoblasts and osteoclasts in post natal life. However the precise mechanism leading to osteoporosis and other manifestations in HCS is unclear [3]. It has autosomal dominant inheritance. Many cases however occur due to spontaneous mutation. Severity of disease and age at diagnosis varies. The diagnosis is made earlier in childhood in patients with family history. However, most often it is diagnosed in adolescence or adulthood.

Clinical Features

At birth, child has dysmorphic features. However these are not characteristic of HCS. As child grows the characteristic features of HCS become more obvious. Majority of patients have short stature. Craniofacial abnormalities include frontal bossing, thick bushy eyebrows, and coarse hair, low hairline in forehead and nape, hirsutism, widely spaced eyes with antimongoloid slant, flat nasal bridge, long philtrum, micrognathia, and premature loss of teeth, low set ears, and short web neck. Patient may complain of frontal and occipital headache due to basilar invagination. Patient may have conductive or sensorineural hearing loss, optic atrophy and optic disc edema. Voice is deep, hoarse and low pitch. Patient may present with pain and shortening of fingers of hand and feet. Fingers appear short and stubby (pseudoclubbing).

Manifestations in other systems include recurrent respiratory tract infections, congenital heart diseases such as atrial septal defect, ventricular septal defect, patent ductus arteriosus, mitral regurgitation and polycystic kidney disease. When polycystic kidney disease is associated with serpentine fibulae, the combination is called Serpentine Fibula Polycystic Kidney Syndrome (SFPKS) [4].

Patient may present with fractures, spinal cord compression, ventilatory restriction, hydrocephalus, tonsillar herniation and syringohydromyelia.

Imaging Features

Characteristic radiological manifestations are seen in skull, hands and feet.

There is delayed closure of sutures, persistent wormian bones especially in lambdoid suture, dolicocephaly, bulging of squamous occipital bone (bathrocephaly), elongated enlarged J shaped sella, aplasia of frontal sinus, platybasia with or without basilar invagination, thickening of skull base and mastoids. Malalignment of teeth, premature loss of teeth due to periodontal disease and resorption of alveolar processes, hypoplastic maxilla, mandible and wide mandibular angle are associated problems. Spine may show osteoporosis, biconcave vertebrae (fish vertebrae), compression fractures, spondylolisthesis and kyphoscoliosis. Hands and feet show two patterns of acro-osteolysis. Characteristic transverse band of osteolysis involving the distal phalanges and distal to proximal type of osteolysis [5] are seen. Joint laxity and subluxations are also noted. In SFPKS, which is also a manifestation of HCS, there is elongation, widening and marked medial bowing of fibulae. Sometimes longitudinal bony striations are seen in ends of long bones. Renal USG shows multiple small cysts in both cortex and medulla. Dual energy X- ray absorptiometry scanning shows decreased bone mineral density compared to normal age and gender matched population. There may be increase in alkaline phosphatase. No other specific biochemical abnormality is detected.

Diagnosis

The diagnosis of this syndrome is based on characteristic clinical features and imaging findings in hands, feet and skull. Presence of positive family history makes diagnosis easier. After the role of truncating mutation in terminal exon of NOTCH 2 became known the gold standard of diagnosis came to rely on demonstration of this mutation.

Treatment

At present there is no specific treatment for Hajdu-Cheney syndrome. Management is symptomatic aimed at preventing osteoporosis. Medical treatment includes bisphosphonate and vitamin D therapy. However, the actual benefit is not proven [5].

Prognosis and Complications

HCS can lead to serious consequences. Osteoporosis is progressive and can cause neurological complications due to basilar invagination and ventilatory restriction due to kyphoscoliosis.

Differential Diagnosis

HCS must be differentiated radiologically from other causes of acro-osteolysis such as hyperparathyroidism, scleroderma, psoriasis, pyknodysostosis, neuropathic (leprosy and diabetes), infective, frost bite, burns, Raynaud's phenomenon, polyvinyl chloride and ergot toxicity and progeria [6].

In hyperparathyroidism there is subperiosteal bone resorption involving radial aspect of middle phalanges of second and third fingers, acro-osteolysis and erosion of medial metaphysis of proximal humerus, femur and tibia.

In scleroderma characteristic soft tissue findings include soft tissue atrophy and calcification in fingertips, peribursal and peritendinous locations. Bone erosion occurs at distal phalanges caused by pressure phenomenon due to soft tissue contractures.

Psoriatic arthropathy usually follows skin changes. Classically there is involvement of distal interphalangeal joint with cartilage loss, malalignment and ankylosis. Fusiform swelling of entire digit 'sausage digit' is characteristic.

Neuropathic joint will show severe malalignments and bone destruction leading to pencilling of phalanges. Bone mineral density is maintained. Vascular calcification may be seen.

The characteristic feature in progeria is accelerated aging, which may be up to seven times the chronological age and short life span (average 7 to 27 years).

Pyknodysostosis is characterised by generalised increase in bone density, straight mandibular angle, prognathism, hypoplasia and resorption of lateral end of clavicles.

Rothmund Thompson's syndrome may have many similarities with HCS but differentiating features include abnormal vertical and horizontal trabeculations in metaphysis of long bones, hypoplasia and fusion of long bones, radial ray anomaly and brachymesophalangy. It is caused by RECQL4 mutation.

The combination of characteristic clinical features, family history, radiographic features of transverse band acro-osteolysis, wormian bones, dental abnormalities and other features help to diagnose HCS, which can now be confirmed by genetic analysis for NOTCH 2 mutation.

TEACHING POINT

Hajdu-Cheney syndrome is a very rare inherited connective tissue disorder characterised by transverse acro-osteolysis, dental abnormalities, wormian bones and osteoporosis. It is important to be aware of this rare disorder and distinguish it from other common conditions that cause acro-osteolysis and bone softening.

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FIGURES

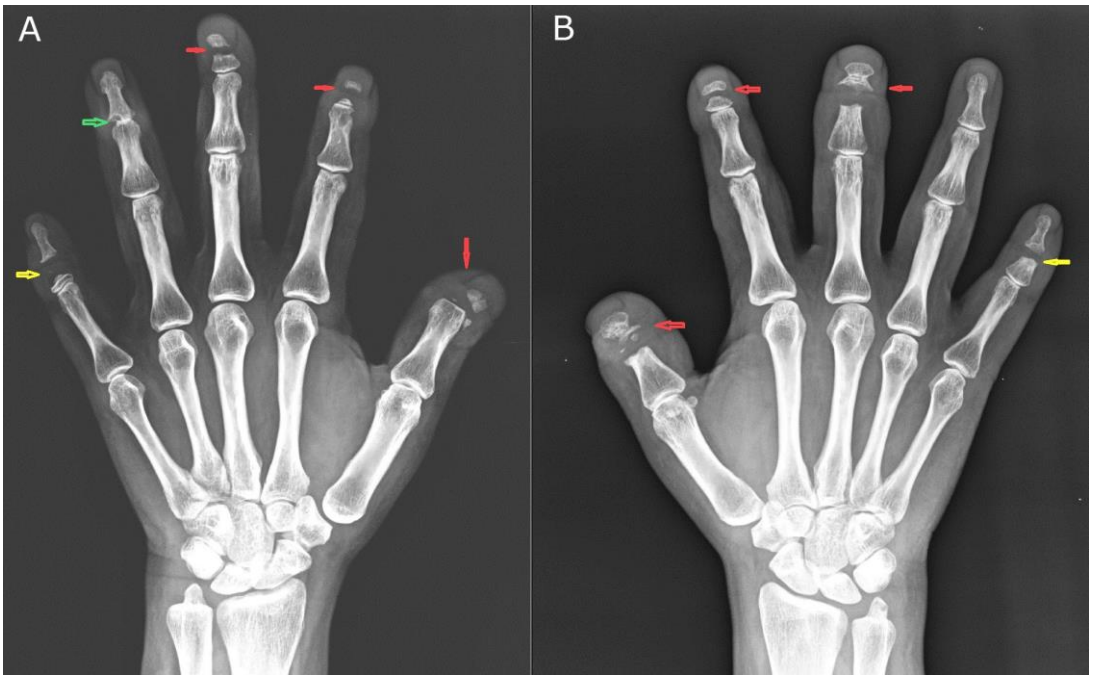

Figure 1: 43-year-old female patient with Hajdu-Cheney syndrome.
Frontal radiograph of right hand (A) shows transverse band of osteolysis involving distal phalanx of second and third finger and middle phalanx of fifth finger. There is near complete osteolysis of distal phalanx of thumb. Marginal erosion is noted at distal interphalangeal joint of fourth finger. Radiograph of left hand (B) shows transverse osteolysis involving distal phalanx of thumb, second and third finger and middle phalanx of fifth finger. The fourth finger is spared. The soft tissues around the tips of terminal phalanges of both hands appear normal. No periarticular or any soft tissue calcification is seen in both hands.

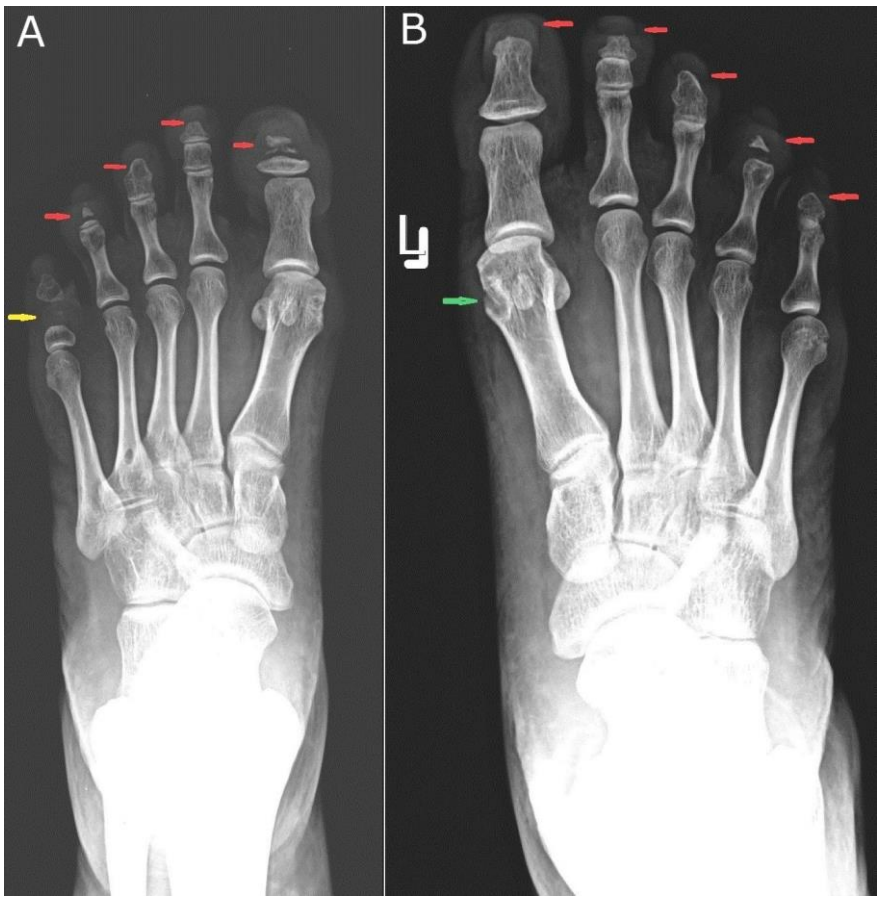

Figure 2 (left): 43-year-old female patient with Hajdu-Cheney syndrome.
Frontal radiograph of right foot (A) shows osteolysis involving distal phalanx of first to fourth toe and middle phalanx of fifth toe.

Frontal radiograph of left (B) foot shows osteolysis involving the distal phalanges of all toes and periarticular erosion at first metatarsophalangeal joint. The soft tissues around the tips of terminal phalanges of both feet appear normal. No periarticular or any soft tissue calcification is seen in both feet.

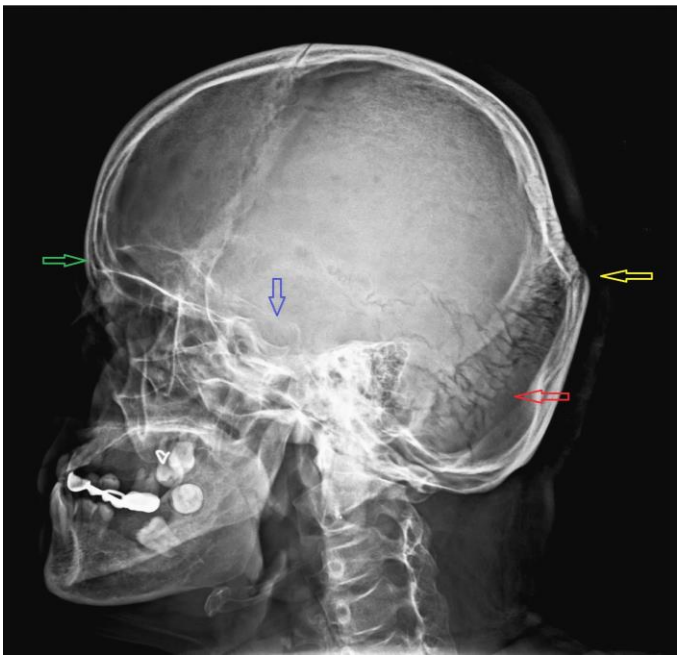

Figure 3: 43-year-old female patient with Hajdu-Cheney syndrome.
Lateral radiograph of skull shows multiple wormian bones in the lambdoid suture. There is mild prominence of squamous occipital bone suggestive of bathrocephaly. There is also aplasia of frontal sinus and elongated J shaped sella.

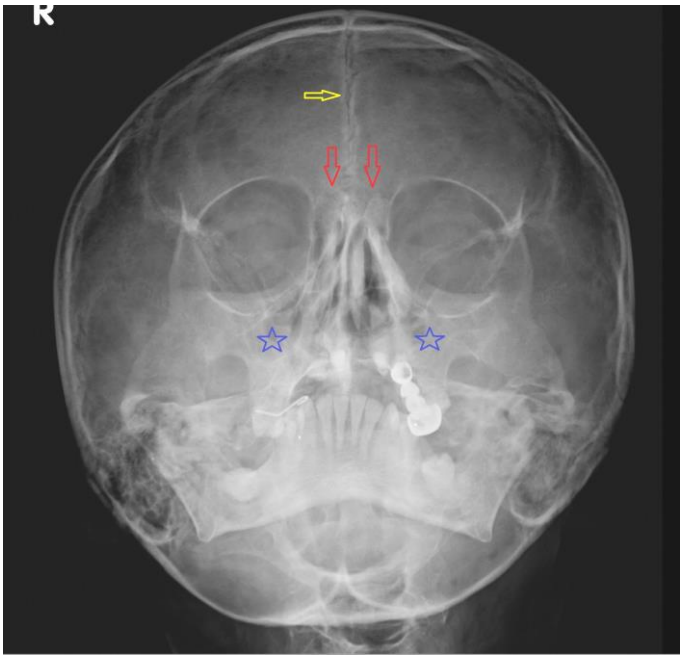

Figure 4: 43-year-old female patient with Hajdu-Cheney syndrome.
Waters view for paranasal sinuses shows aplastic frontal sinus with markedly hypoplastic maxillary sinuses bilaterally. Unfused metopic suture is also noted.

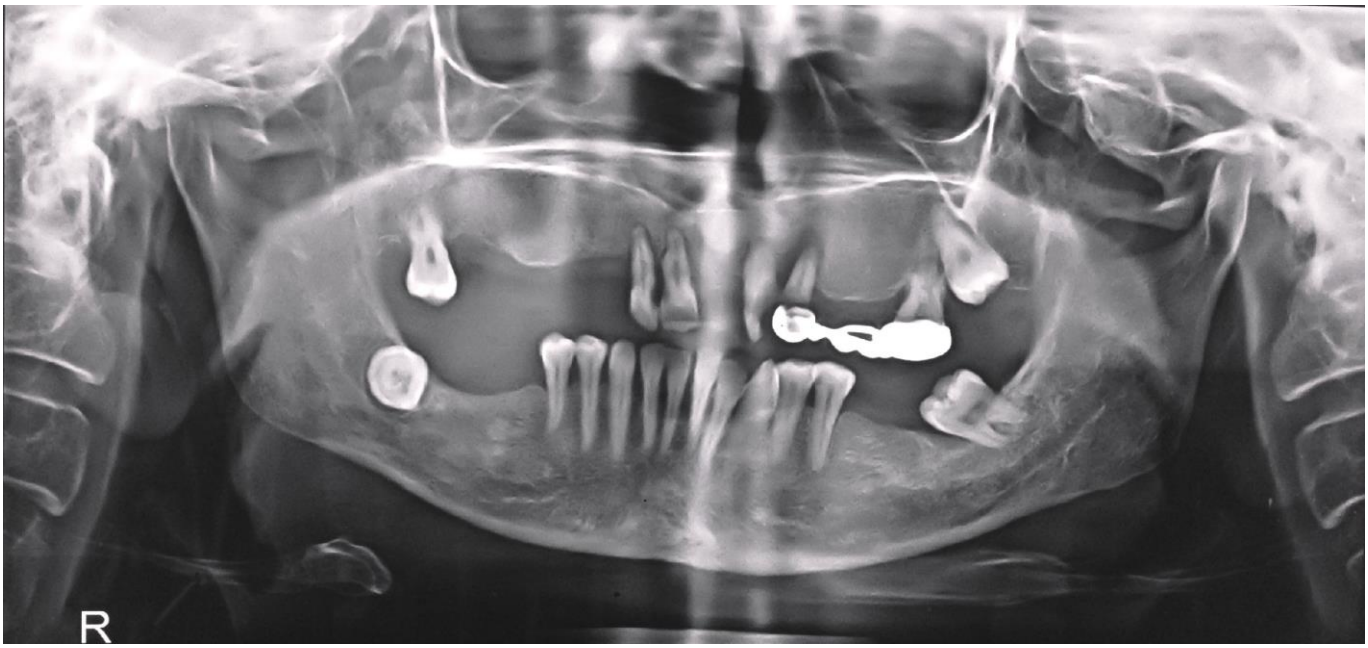

Figure 5: 43-year-old female patient with Hajdu-Cheney syndrome.
Orthopentomogram shows erosion of alveolar margin of maxilla and mandible with loss of multiple upper and lower teeth. The residual teeth show loss of lamina dura around them. Dental prosthesis is also noted.

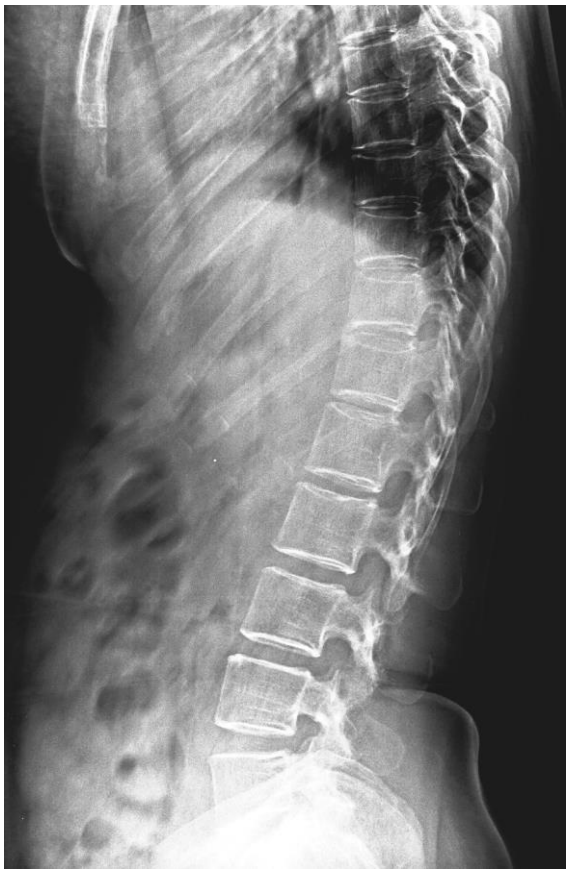

Figure 6: 43-year-old female patient with Hajdu-Cheney syndrome.
Lateral radiograph of spine shows mild osteoporosis of dorso-lumbar vertebrae. No osteoporotic compression of vertebrae is seen.

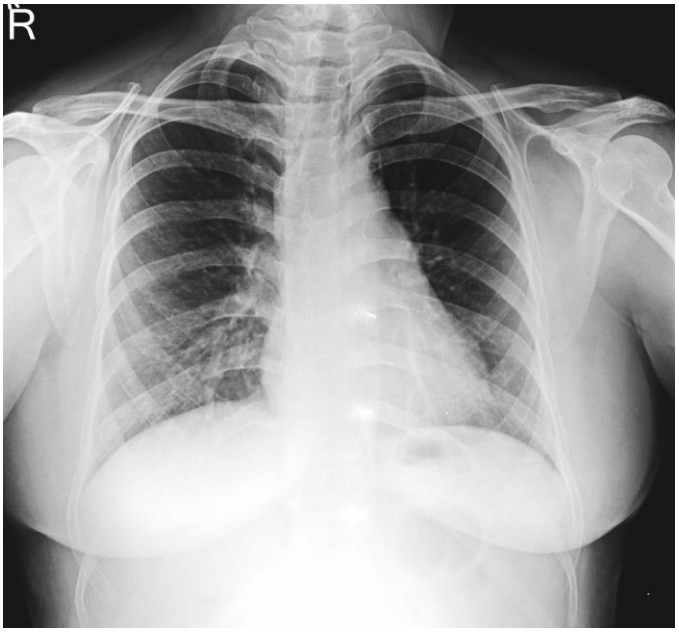

Figure 7: 43- year-old female patient with Hajdu-Cheney syndrome.
Posteroanterior radiograph of chest does not show any obvious abnormality.

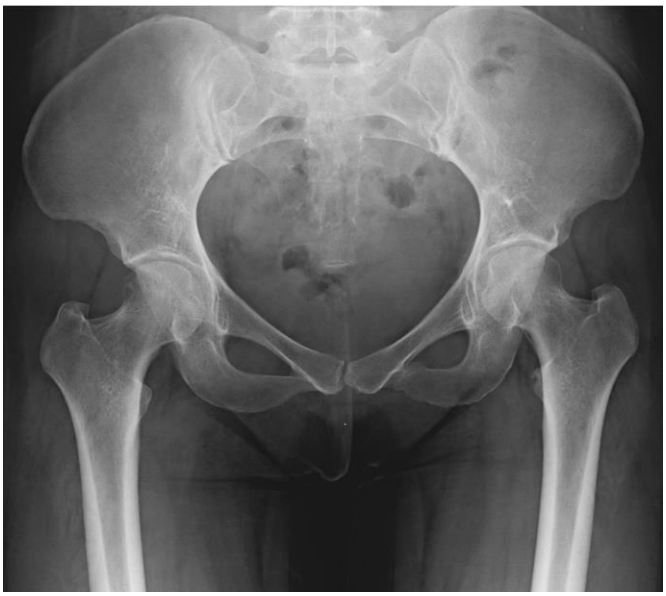

Figure 8: 43-year-old female patient with Hajdu-Cheney syndrome.
Anteroposterior radiograph of pelvis is unremarkable.

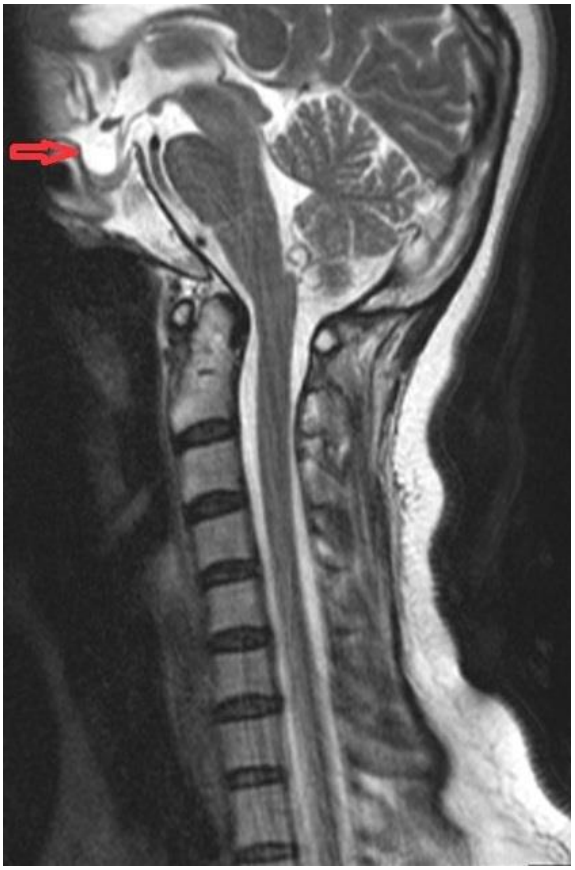

Figure 9: 43-year- old female patient with Hajdu-Cheney syndrome.
T2W sagital image (1.5T MRI, TR 3200, TE 96, slice thickness 5mm) shows partially empty sella. No basilar invagination or any other abnormality seen.

Entity	General features	Radiological features
Hajdu-Cheney syndrome	• Shortening of fingers and toes • Premature loss of teeth • Alkaline phosphatase may be increased • No other hormonal or biochemical abnormality	• Transverse acro-osteolysis • Dental malalignment and premature loss of teeth • Hypoplastic maxilla and mandible • Hypoplastic/ aplastic frontal sinus • Enlarged J shaped sella • Delayed closure of sutures • Wormian bones • Bathrocephaly • Dolicocephaly • Platybasia • Basilar invagination • Kyphoscoliosis • Joint laxity and subluxations
Hyperparathyroidism	• Primary or secondary • Increased PTH levels	• Subperiosteal cortical erosion in radial aspect of middle phalanges of second and third fingers • Acro-osteolysis • Erosion of medial metaphysis of humerus, femur and tibia
Scleroderma	• Multisystem autoimmune connective tissue disorder	• Musculoskeletal- acro-osteolysis, subcutaneous and periarticular calcification, atrophy at finger tips • Pulmonary- NSIP or UIP pattern • Gastrointestinal- dilatation of distal 2/3rd of oesophagus, hidebound bowel sign
Psoriatic arthritis	• Seronegative spondyloarthritis • Arthropathy usually follows skin manifestations	• Erosion, malalignment and ankylosis in distal interphalyngeal joint • Sausage digit • Periostitis • Sacroilitis • Asymmetric paravertebral ossifications
Neuropathic (diabetes, leprosy)	• Uncontrolled diabetes of long duration • Feet more commonly involved	• Severe bone destruction • Malalignments • Pencilling of phalanges • Bone mineral density is maintained • Vascular calcification
Pyknodysostosis	• Autosomal recessive • Short stature • Multiple bone fractures	• Generalised increase in bone density- osteosclerosis • Acro-osteolysis • Obtuse mandibular angle • Wormian bones • Delayed closure of sutures • Hypoplastic clavicle
Progeria	• Accelerated aging • short life span	• Acro-osteolysis • Delayed closure of sutures • Wormian bones • Hypoplastic maxilla and mandible • Fish mouth vertebrae • Coxa valga
Rothmund-Thompson's syndrome	• Autosomal recessive • Poikiloderma- characteristic rash in infancy • Sparse hair eyelashes and eyebrows • Short stature • RECQL4 mutation	• Radial ray anomaly • Brachymesophalangy • Abnormal vertical and horizontal trabeculations in metaphysis of long bones • Hypoplasia and fusion of long bones

Table 1: Differential diagnosis table for Hajdu-Cheney syndrome

Etiology	Mutation in terminal exon of NOTCH 2
Inheritance	Autosomal dominant or spontaneous de novo mutation
Incidence	Very rare (about fifty cases are reported in literature)
Gender ratio	No gender predilection
Age at diagnosis	Childhood in presence of family history, otherwise most often diagnosed in adolescence or adulthood
Clinical features	Skeletal, craniofacial and dental abnormalities
Imaging findings	• Skull and mandible – delayed closure of sutures, wormian bones, bathrocephaly, dolicocephaly, platybasia, basilar invagination, enlarged J shaped sella, aplastic/ hypoplastic frontal sinuses, thickening of calvarium, hypoplastic maxilla and mandible, malalignment and premature loss of teeth • Spine - biconcave(fish vertebrae), anterior wedging, compression, spondylolisthesis, kyphoscoliosis • Hands and feet – transverse band osteolysis, distal to proximal osteolysis involving phalanges, joint laxity • Long bones – serpentine fibulae, longitudinal striations, hypoplastic distal radius, joint laxity • Other systems – Renal system – polycystic kidney disease (serpentine fibula polycystic kidney syndrome ; SFPKS) • Cardiovascular system – congenital heart diseases – atrial and ventricular septal defects, patent ductus arteriosus, mitral regurgitation • Gastrointestinal system – gut malrotation • Respiratory system – recurrent infections, ventilatory restriction due to kyphoscoliosis
Biochemical	Raised alkaline phosphatase, No other specific biochemical abnormality
Diagnosis	Clinical features, family history and characteristic imaging features in hands and skull; gold standard for diagnosis is genetic analysis for NOTCH 2 mutation
Treatment	Symptomatic – bisphosphonates, vitamin D and surgical treatment of complications
Prognosis	Progressive disorder with serious consequences
Complications	Neurological complications due to basilar invagination and kyphoscoliosis, ventilatory restriction due to kyphoscoliosis and fractures

Table 2: Summary table for Hajdu-Cheney syndrome

ABBREVIATIONS

HCS = Hajdu-Cheney syndrome
MRI = Magnetic resonance imaging
SFPKS = Serpentine Fibula Polycystic Kidney Syndrome

KEYWORDS

Hajdu-Cheney syndrome; Acro-osteolysis; wormian bones; acro-dento-osteo-dysplasia; NOTCH 2

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