= Osteitis fibrosa cystica =

Osteitis fibrosa cystica / ??sti??a?t?s fa??bro?s? ?s?st?k? / , abbreviated OFC , also known as osteitis fibrosa , osteodystrophia fibrosa , and Von Recklinghausen 's disease of bone (not to be confused with Von Recklinghausen 's disease , neurofibromatosis type I) , is a skeletal disorder caused by hyperparathyroidism , which is a surplus of parathyroid hormone from over @-@ active parathyroid glands . This surplus stimulates the activity of osteoclasts , cells that break down bone , in a process known as osteoclastic bone resorption . The hyperparathyroidism can be triggered by a parathyroid adenoma , hereditary factors , parathyroid carcinoma , or renal osteodystrophy . Osteoclastic bone resorption releases minerals , including calcium , from the bone into the bloodstream . In addition to elevated blood calcium levels , over @-@ activity of this process results in a loss of bone mass , a weakening of the bones as their calcified supporting structures are replaced with fibrous tissue (peritrabecular fibrosis) , and the formation of cyst @-@ like brown tumors in and around the bone . The symptoms of the disease are the consequences of both the general softening of the bones and the excess calcium in the blood , and include bone fractures , kidney stones , nausea , moth @-@ eaten appearance in the bones , appetite loss , and weight loss .

First described in the nineteenth century , OFC is currently detected through a combination of blood testing , X @-@ rays , and tissue sampling . Before 1950 , around half of those diagnosed with hyperparathyroidism in the United States saw it progress to OFC , but with early identification techniques and improved treatment methods , instances of OFC in developed countries are increasingly rare . Where treatment is required , it normally involves addressing the underlying hyperparathyroidism before commencing long @-@ term treatment for OFC ? depending on its cause and severity , this can range from hydration and exercise to surgical intervention .

= = Classification = =

Osteitis fibrosa cystica is defined as the classic skeletal manifestation of advanced hyperparathyroidism . Under the ICD @-@ 10 classification system , established by the World Health Organization , OFC is listed under category E21.0 , primary hyperparathyroidism .

= = Signs and symptoms = =

The major symptoms of OFC are bone pain or tenderness , bone fractures , and skeletal deformities such as bowing of the bones . The underlying hyperparathyroidism may cause kidney stones , nausea , constipation , fatigue and weakness . X @-@ rays may indicate thin bones , fractures , bowing , and cysts . Fractures are most commonly localized in the arms , legs , or spine .

The addition of weight loss , appetite loss , vomiting , polyuria , and polydipsia to the aforementioned symptoms may indicate that OFC is the result of parathyroid carcinoma . Parathyroid carcinoma , an uncommon cancer of the parathyroid glands , is generally indicated by serum calcium levels higher than usual , even in comparison to the high serum calcium levels that OFC generally presents with . Symptoms are also often more severe . Generally , the presence of a palpable neck mass is also indicative of the cancer , occurring in approximately 50 % of sufferers , but virtually nonexistent in individuals with OFC with a different origin .

= = Causes = =

Osteitis fibrosa cystica is the result of unchecked hyperparathyroidism , or the overactivity of the parathyroid glands , which results in an overproduction of parathyroid hormone (PTH) . PTH causes the release of calcium from the bones into the blood , and the reabsorption of calcium in the kidney . Thus , excess PTH in hyperparathyroidism causes elevated blood calcium levels , or hypercalcemia . There are four major causes of primary hyperparathyroidism that result in OFC :

Parathyroid Adenoma

The vast majority of cases of hyperparathyroidism are the result of the random formation of benign , but metabolically active , parathyroid adenoma swellings . These instances comprise approximately 80 ? 85 % of all documented cases of hyperparathyroidism .

Hereditary factors

Approximately 1 in 10 documented cases of hyperparathyroidism are a result of hereditary factors . Disorders such as familial hyperparathyroidism , multiple endocrine neoplasia type 1 (MEN Type 1) and hyperparathyroidism @-@ jaw tumor syndrome can , if left unchecked , result in OFC . MEN Type 1 is an autosomal dominant disorder and the most common hereditary form of hyperparathyroidism , affecting about 95 % of genetic cases of OFC , and also tends to affect younger patients than other forms . Major mutations which can lead to hyperparathyroidism generally involve the parathyroid hormone receptor , G proteins , or adenylate cyclase . Certain genetic mutations have been linked to a higher rate of parathyroid carcinoma occurrence , specifically mutations to the gene HRPT2 , which codes for the protein parafibromin .

Parathyroid carcinoma

Parathyroid carcinoma (cancer of the parathyroid gland) is the rarest cause of OFC , accounting for about 0 @.@ 5 % of all cases of hyperparathyroidism . OFC onset by parathyroid carcinoma is difficult to diagnose .

Renal complications

OFC is a common presentation of renal osteodystrophy , which is a term used to refer to the skeletal complications of end stage renal disease (ESRD) . OFC occurs in approximately 50 % of patients with ESRD . ESRD occurs when the kidneys fail to produce calcitriol , a form of Vitamin D , which assists in the absorption of calcium into the bones . When calcitriol levels decrease , parathyroid hormone levels increase , halting the storage of calcium , and instead triggering its removal from the bones . The concept of renal osteodystrophy is currently included into the broader term chronic kidney disease @-@ mineral and bone disorder (CKD @-@ MBD) .

= = Pathophysiology = =

The effects of OFC on bone are largely dependent on the duration of the disease and the level of parathyroid hormone (PTH) produced . PTH is responsible for maintaining a homeostatic calcium concentration in the blood . It activates the parathyroid @-@ hormone related protein receptor located on osteoblasts and osteocytes , both of which are responsible for the building and calcification of bone . Abnormalities affecting the parathyroid glands cause a surplus of PTH , which , in turn , increases the activity and frequency of osteoblasts and osteocytes . Increased PTH levels trigger the release of stored calcium through the dissolution of old bone , as well as the conservation of serum calcium through a cessation in the production of new bone .

Generally , the first bones to be affected are the fingers , facial bones , ribs , and pelvis . Long bones , which are longer than they are wide , are also among the first affected . As the disease progresses , any bone may be affected .

= = Diagnosis = =

OFC may be diagnosed using a variety of techniques . Muscles in patients afflicted with OFC can either appear unaffected or " bulked up . " If muscular symptoms appear upon the onset of hyperparathyroidism , they are generally sluggish contraction and relaxation of the muscles . Deviation of the trachea (a condition in which the trachea shifts from its position at the midline of the neck) , in conjunction with other known symptoms of OFC can point to a diagnosis of parathyroid carcinoma .

Blood tests on patients with OFC generally show high levels of calcium (normal levels are considered to range between 8 @.@ 5 and 10 @.@ 2 mg / dL , parathyroid hormone (levels generally above 250 pg / mL , as opposed to the " normal " upper @-@ range value of 65 pg / mL) , and alkaline phosphatase (normal range is 20 to 140 IU / L) .

X @-@ rays may also be used to diagnose the disease . Usually , these X @-@ rays will show

extremely thin bones , which are often bowed or fractured . However , such symptoms are also associated with other bone diseases , such as osteopenia or osteoporosis . Generally , the first bones to show symptoms via X @-@ ray are the fingers . Furthermore , brown tumors , especially when manifested on facial bones , can be misdiagnosed as cancerous . Radiographs distinctly show bone resorption and X @-@ rays of the skull may depict an image often described as " ground glass " or " salt and pepper " . Dental X @-@ rays may also be abnormal .

Cysts may be lined by osteoclasts and sometimes blood pigments , which lend to the notion of " brown tumors . " Such cysts can be identified with nuclear imaging combined with specific tracers , such as sestamibi . Identification of muscular degeneration or lack of reflex can occur through clinical testing of deep tendon reflexes , or via photomotogram (an achilles tendon reflex test) .

Fine needle aspiration (FNA) can be used to biopsy bone lesions , once found on an X @-@ ray or other scan . Such tests can be vital in diagnosis and can also prevent unnecessary treatment and invasive surgery . Conversely , FNA biopsy of tumors of the parathyroid gland is not recommended for diagnosing parathyroid carcinoma and may in fact be harmful , as the needle can puncture the tumor , leading to dissemination and the possible spread of cancerous cells .

The brown tumors commonly associated with OFC display many of the same characteristics of osteoclasts . These cells are characteristically benign , feature a dense , granular cytoplasm , and a nucleus that tends to be ovular in shape , enclosing comparatively fine chromatin . Nucleoli also tend to be smaller than average .

= = Management = =

= = = Medical = = =

Medical management of OFC consists of Vitamin D treatment , generally alfacalcidol or calcitriol , delivered intravenously . Studies have shown that in cases of OFC caused by either end @-@ stage renal disease or primary hyperparathyoidism , this method is successful not only in treating underlying hyperparathyoidism , but also in causing the regression of brown tumors and other symptoms of OFC .

= = = Surgery = = =

In especially severe cases of OFC , parathyroidectomy , or the full removal of the parathyroid glands , is the chosen route of treatment . Parathyroidectomy has been shown to result in the reversal of bone resorption and the complete regression of brown tumors . In situations where parathyroid carcinoma is present , surgery to remove the tumors has also led to the regression of hyperparathyroidism as well as the symptoms of OFC .

Bone transplants have proven successful in filling the lesions caused by OFC . A report showed that in 8 out of 11 instances where cavities caused by OFC were filled with transplanted bone , the lesion healed and the transplanted bone blended rapidly and seamlessly with the original bone .

= = Prognosis = =

Almost all who undergo parathyroidectomy experience increased bone density and repair of the skeleton within weeks . Additionally , patients with OFC who have undergone parathyroidectomy begin to show regression of brown tumors within six months . Following parathyroidectomy , hypocalcaemia is common . This results from a combination of suppressed parathyroid glands due to prolonged hypercalcaemia , as well as the need for calcium and phosphate in the mineralization of new bone .

Thirty percent of patients with OFC caused by parathyroid carcinoma who undergo surgery see a local recurrence of symptoms . The post @-@ surgical survival rate hovers around seven years , while patients who do not undergo surgery have a survival rate of around five years .

= = Epidemiology = =

Osteitis fibrosa cystica has long been a rare disease . Today , it appears in only 2 % of individuals diagnosed with primary hyperparathyroidism , which accounts for 90 % of instances of the disease . Primary hyperparathyroidism is three times as common in individuals with diabetes mellitus .

The hospitalization rate for hyperparathyroidism in the United States in 1999 was 8 @.@ 0 out of 100 @,@ 000 . The disease has a definite tendency to affect younger individuals , typically appearing before the age of 40 , with a study in 1922 reporting that 70 % of cases display symptoms before the age of 20 , and 85 % before 35 . Primary hyperparathyoidism , as well as OFC , is more common in Asiatic countries . Before treatment for hyperparathyroidism improved in the 1950s , half of those diagnosed with hyperparathyroidism saw it progress into OFC .

Rates of OFC increase alongside cases of unchecked primary hyperparathyroidism . In developing countries , such as India , rates of disease as well as case reports often mirror those published in past decades in the developed world .

The other 10 % of cases are primarily caused by primary hyperplasia , or an increase of the number of cells . Parathyroid carcinoma accounts for less than 1 % of all cases , occurring most frequently in individuals around 50 years of age (in stark contrast to OFC as a result of primary hyperparathyroidism) and showing no gender preference . Approximately 95 % of hyperparatyhroidism caused by genetic factors is attributed to MEN type 1 . This mutation also tends to affect younger individuals .

= = History = =

The condition was first described by Gerhard Engel in 1864 and Friedrich Daniel von Recklinghausen in 1890 , though William Hunter , who died in 1783 , is credited with finding the first example of the disease . " von Recklinghausen 's disease " (without the qualification " of bone ") is a completely unrelated disorder , nowadays termed neurofibromatosis . In 1884 , Davies Colley delivered a presentation to the Pathological Society of London that detailed the manifestation of hyperparathyroidism into a brown tumor of the mandible , as well as the histological makeup of the tumor .

The discovery and subsequent description of the parathyroid glands is credited to Ivar Sandstrom , though his publication , On a New Gland in Man and Several Mammals @-@ Glandulae Parathyroideae , received little attention . Gustaf Retzius and Eugene Gley compounded his research , the latter credited with the discovery of the function of the parathyroid glands . This research cumulated in the first surgical removal of a parathyroid tumor by Felix Mandel in 1925 . A 2 @.@ 5 × 1 @.@ 5 @-@ inch (64 × 38 mm) tumor was removed from the thyroid artery of a man suffering from advanced OFC . The patient 's symptoms disappeared , only to return in approximately six years as a result of renal stones that were diagnosed only after the patient had died . In 1932 , blood tests on a female patient suffering from renal stone @-@ based OFC revealed extremely high blood calcium levels . Fuller Albright diagnosed and treated the woman , who suffered from a large tumor of the neck as well as renal stones .

The first published literature to describe a brown tumor (which was linked to OFC) was published in 1953 , though clinical reports from before 1953 do draw a correlation between the disease and tumors previous to the publication .

The advent of the multichannel autoanalyzer in the 1960s and 70s led to an increase in early diagnosis of primary hyperparathyroidism . This increase led to a sharp decline in the prolonged manifestation of the disease , leading to a drop in the number of cases of OFC due to the early detection of hyperparathyroidism . Before this invention , the diagnosis of primary hyperparathyroidism was generally prolonged until the emergence of severe manifestations , such as OFC .