

Research Article

Etiology Understanding Is the Core of Skeletal Diagnosis

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Abstract

Background: The term idiopathic is a non-specific disease label, which fails account for proper etiological understanding. The frequent usage of the term idiopathic may indicate clinical incompetence. We describe a number of patients from our practice with a history of complex bone disorders who were falsely given the term idiopathic by other Institutes. The sole tool used by other Institutes to conclude osteoporosis as a diagnosis is the bone mineral density.

Material and Methods: Two Austrian families and one unrelated adult female patient (total number of 12 subjects) have been referred to our department with referral letters confirming the diagnosis of idiopathic osteoporosis. All patients manifested a diverse constellation of skeletal deformities. In all these patients, regular courses of anti-resorptive treatment plus calcium and vitamin D supplements. These have been excessively prescribed.

Results: Our diagnostic process was based heavily on detailed clinical and radiological phenotypic characterizations, we refuted the diagnosis of idiopathic osteoporosis for all patients because of the clear-cut clinical features. For the first family, we suggested the diagnosis of a novel type of mucopolysaccharidosis. The genetic results confirmed the diagnosis of a novel subtype of mucopolysaccharidosis through the identification of arylsulfatase K deficiency (ARSK-gene). For the second family which has been subjected to a lengthy useless investigation for almost more than a decade, we refuted the diagnosis of idiopathic osteoporosis and the whole exome sequencing was consistent with the phenotypic diagnosis Nasu-Hakola disease (heterozygous missense mutations in TYROBP gene). The other unrelated 42-year-old- female patient was correctly diagnosed with Nasu-Hakola disease.

Conclusion: The objective of this study is to minimize and suppress the usage of the term idiopathic. It has been imperative to understand the sequence of pathological events that occurred in these families. The core for diagnosis is the etiological understanding, which stemmed from professional conscientiousness. Patients underwent misdiagnosis of idiopathic osteoporosis and were treated extensively with anti-resorptive agents, calcium supplements and vitamin D. Strikingly, these

medications resulted in a combination of serious cranial and cerebral lesions because of massive pathological calcifications. Imaging analysis via conventional radiographs, MRI and CT scan showed massive calcifications of the cranial sutures, inter-clinoid ligaments and hyper-calcification of the skull base. Sadly speaking, early onset dementia emerged in connection with sclerosing leukoencephalopathy. We believe that the exogenous toxic effects of the huge amounts of bone supplements consumed by these patients enhanced the pre-existing metabolic bone and cerebral disorders. Our findings can ameliorate the etiological understanding of early onset dementia and other correlated cranial and skeletal lesions.

Keywords: Idiopathic Osteoporosis; Anti-Resorptives; Calcifications; Mucopolysaccharidosis Type X; Nasu-Hakola Disease; Radiology; CT Scan

Introduction

Patients who were given false diagnosis of certain long term skeletal or extra-skeletal abnormalities have been unfortunate.

When a certain medical discipline fails to identify correct diagnosis, this sort of malpractice is often the result of insufficient knowledge and experience. False diagnosis under what's called idiopathic can easily lead to a long-term morbid or mortal complication. The impact on the patient's life and their families can be devastating. Misdiagnosis has been the core of discussions in a high number of studies worldwide. International studies focused mainly on the most common diagnostic errors which are correlated with vascular diseases, myocardial infarction, stroke, as well as with less common diseases such as endocarditis, meningitis and encephalitis [1-3]. Care should be taken when using terms such as idiopathic. They only "appear" random or more often named as "idiopathic" because a connection has not been made between the onset of the deformity and, other unseen abnormal features in the same patient or in his siblings, parents and relatives. For the instance we describe two unfortunate families, who underwent a series of sophisticated investigations in other Austrian hospitals for more than a decade and finally the only report they received was "idiopathic osteoporosis". The index case of the first family has been treated in correlation with the primary diagnosis of idiopathic osteoporosis. Courses of anti-resorptive medications in addition to calcium supplements have been administered on regular bases. After performing detailed clinical and radiological interpretations, we totally refuted the diagnosis of idiopathic osteoporosis and we suggested the diagnosis of either a novel type of mucopolysaccharidosis or SPONASTRIM dysplasia [4,5]. The genetic tests confirmed our clinical views and a novel subtype of mucopolysaccharidosis caused by Arylsulfatase K (ARSK) deficiency has been confirmed. All the published photos in this paper are only the photos of the patient of the senior author of this paper (Al Kaissi) [6]. The second family and over three generations experienced tarsal and carpal fractures associated with dementia. The index case has been diagnosed with idiopathic osteoporosis and was treated accordingly with anti-resorptive medications and calcium supplements. His clinical and radiological phenotype have been analyzed by the senior author (Al Kaissi), he showed compatibility with the whole exome sequencing revealed heterozygous missense mutations in TYROBP gene encoding for a cell-surface adaptor protein, which is part of a signaling complex triggering activation of immune responses totally consistent with the diagnosis of Nasu-Hakola syndrome [7,8]. In this paper we discuss the contradictions and the controversies of misdiagnosis and the serious outcome of wrong medications.

Methods

The study protocol was approved by Ethics Committee of the (Ilizarov Scientific Research Institute, No.4(50)/13.12.2016, Kurgan, Russia). The clinical evaluation of the patients has been commenced by the senior author who was totally in charge of the clinical phenotype and interpretations of the radiographs, CT scan and MRI images. Patients were seen at the orthopedic Hospital of Speising (Osteogenetische Ambulanz), Vienna, Austria. Family consents have been given accordingly and through the scientific collaboration of the first author with Ilizarov Center, Kurgan, Russia. Scrutinizing family subjects through the index case (which is the most affected subject) was our baseline tool to fulfil the diagnostic process of every family member. Our efforts directed toward clinical investigations in an ascending manner via the family pedigrees. The strategy of other institutes based primarily on laboratory tests and certain molecular studies in addition to the dual-energy x ray absorptiometry scan. All subjects from the families were investigated for serum calcium, serum phosphate and vitamin D which was assessed via radioimmunoassay, all showed normal results. Serum Crosslaps, PTH, and other endocrinal investigations showed normal levels. The index cases from two families showed no mutations in the COL1A1/COL1A2 gene. At this point, the diagnosis finalized with conclusion of being idiopathic osteoporosis. Anti-resorptive treatment has been administered by other institutes in accordance with the diagnosis of idiopathic osteoporosis. Doses of 20 mg teriparatide (subcutaneous injections) 1-34 and 0.5 mg calcitriol per day were prescribed for 18 months. In addition, oral Calcium supplements has been heavily prescribed with vitamin D. These therapeutic measures showed false improvement of the BMD.

Family I (Diagnosis of a novel sub-type of Mucopolysaccharidosis)

The index case is a 13-year-old girl who was referred to our department because of pain in the hip joints accompanied with a referral letter from a colleague giving the diagnosis of idiopathic osteoporosis. She manifested short stature (short trunk dwarfism-3SD) with protruding sternum, coarse facies (impish facial features with depressed nasal bridge and prominent cheeks and broad anteverted nose). The head looked macrocephalic. Musculoskeletal examination showed no ligamentous hyperlaxity. Family history revealed consanguinity and both parents are from the same geographical origin. The child is with somehow normal intelligence. Radiologic examination: Hands radiographs showed dysplastic, small carpal bones with marked retardation of bone age with metaphyseal irregularities of the distal metacarpophalangeal joints. Lateral skull radiograph showed diffuse calcification of the cranium. She received regular doses of anti-resorptives and calcium supplements to treat the false diagnosis of idiopathic osteoporosis (Fig.1).

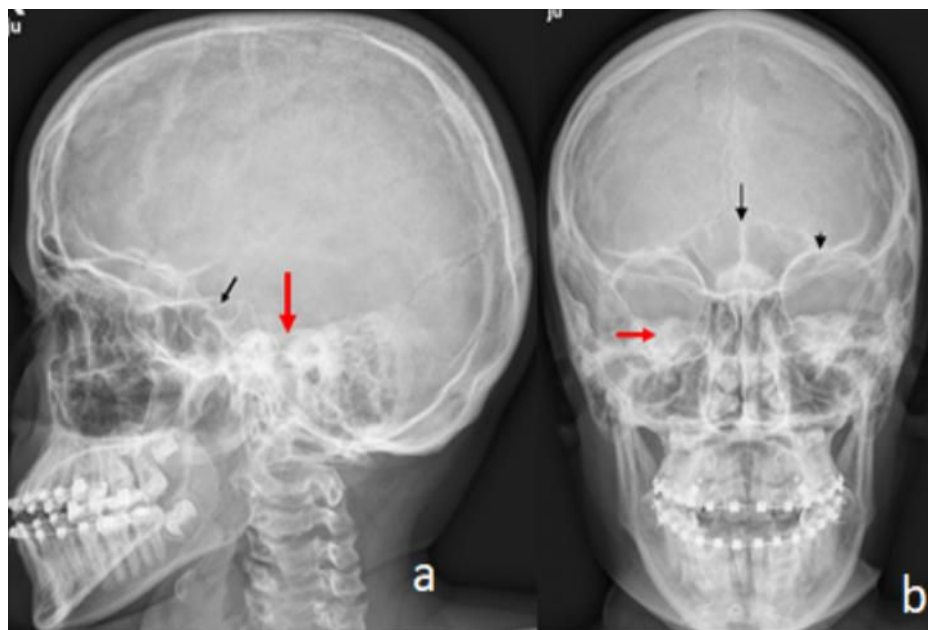


Figure 1: a,b: Lateral skull radiograph of a 13-year-old female showing diffuse calcification of the cranium. Extensive calcium supplements caused pathological calcification of the interclinoid ligament of the sella-turcica (arrow) causing a possible abnormal influence on the blood flow to the left internal carotid artery and even leads to dysfunction of the muscles of the eye owing to possible compression of the oculomotor nerve. Observe the hyperostosis of the skull base (red arrow) which leads to obliteration of the optic and auditory nerves (a); AP skull radiograph of a 13-years-old- female patient showed diffuse calcification of the facial bones and sclerosis of the sagittal suture as well as sclerosis of the rest of the skull sutures. Note extensive calcifications of the glabella (arrow), supraorbital foramina (arrow head), and calcification of the greater wing of the sphenoid bone (red arrow). Calcification of the sphenoid bone leads to obliteration of several blood vessels which conveys blood and nerves to the head and neck (b).

Results

The clinical diagnosis has been established by the senior author at Ortho-Genetic Clinic of the Orthopedic Hospital of Speising, Vienna. The report written by the senior author was a clear cut: Totally Refuted the term idiopathic osteoporosis as has been suggested by another Austrian Medical Centre. The report sent to the genetic Institute of Graz suggested the diagnosis of: A novel type of Mucopolysaccharidosis. The family was referred for genetic analysis to the Institute of Human Genetics, Diagnostic and Research Center for Molecular BioMedicine, Medical University of Graz, Austria. The genetic results confirmed the clinical diagnosis and ARSK has been identified as a candidate gene. Thence fore, the final diagnosis of a novel subtype of mucopolysaccharidosis caused by arylsulfatase K (ARSK) deficiency has been issued.

Family II (Diagnosis: Nasu-Hakola Disease)

The index case is a 34-year-old-man with a history of carpal and tarsal fractures since he was 10-years-old. He spent 24 years seeking diagnosis in different Austrian Medical Institutes. He had a history of painful episodes related to pathologic fractures on minor trauma (particularly the end of the long bones and carpal and tarsal fractures). Family history showed two sisters (one half and one full biological sisters) both had a history of fractures. Parents and grandparents all showed a history of osteoporosis and early dementia. His laboratory findings were non-contributory and no hormonal imbalance was noted. Radiographs showed cystic rarefactions in the epiphyseal regions of bones. Radiographs showed cystic rarefactions in the epiphyseal regions of bones. Though his latest bone mineral density after being treated with calcium supplements and courses of anti-resorptive medications showed confusing results. Despite the improvement in his BMD bone mineral density as measured by DEXA (dual X-ray absorptiometry), which revealed increased density in spine (L1-L4 T-score 2.7) and femoral neck (T-score 1.1). But nevertheless, his cranial bones and cerebral lesions underwent a vicious pathological ossification. In other words, the latest DEXA figures were misleading (Fig. 2, Table 1).

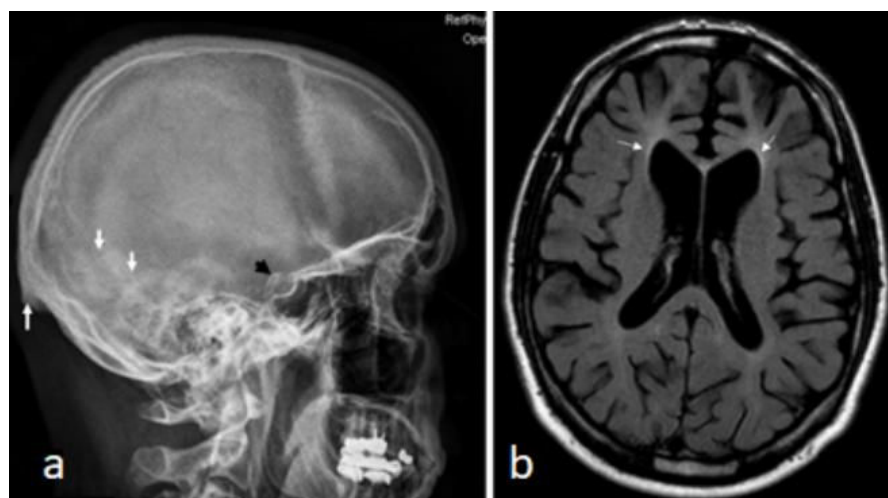


Figure 2: a,b: Lateral skull radiograph of a 34-year-old male patient who received extensive treatment with calcium supplements and courses of anti-resorptives aiming to lessens his fracture rate. The pathological effect of the calcium supplementations was evident through the pathological calcification of the interclinoid ligament of the sella-turcica (black arrow) causing abnormal influence on the blood flow to the left internal carotid artery and even leads to dysfunction of the muscles of the eye owing to possible compression of the oculomotor nerve. In addition, diffuse ossification of the lambdoid sutures altering the physiological flexibility of these sutures into a rigid ankylosed sutures. Ankylosed sutures are prone to fractures regardless the magnitude of trauma, which can rip the meningeal artery (particularly the middle meningeal artery). Bleeding can lead to the development of an epidural hematoma. The aftermath of such incident causing increased intracranial pressure and hazardous brain herniation can occurs (specifically through the edge of the tentorium cerebelli). Furthermore, note the development of an occipital spur which signifies ossification and enthesopathy of the ligamentum nucha secondary to extensive treatment and calcium supplementation (arrow). Magnetic Resonance Image (MRI) of the brain from the index case with Nasu-Hakola disease. Fluid-Attenuated Inversion Recovery (FLAIR) sequence MRI showing periventricular Sclerosing Leukoencephalopathy (b) (white arrows) (b).

Patient	First Presentation	Radiographic Phenotype and Treatment	Neurological Manifestations	Genotype
Proband (Male) 34-year-old	10 yrs-Tarsal fractures	CT scan: cystic like osteolytic lesions in talus and calcaneus. Received antiresorptive treatment and calcium supplements	Euphoria and early dementia	c.94G>A/c.167T>C*
Mother 58-year-old	Kyposcoliosis	Osteoporosis received calcium supplementst	Dementia	N/c.167T>C
Father 64-year-old	Thoraco-lumbar scoliosis	Osteoporosis received calcium supplements	Dementia	N/c.94G>A
Sister 42-year-old	12 yrs-Tarsal fractures	Osteolytic lesions talus and calcaneus	No neurological symptoms yet	N/c.167T>C
Half Sister 39-year-old	9 yrs-Tarsal fractures	Ostelytic lesions talus and calcaneus	Euphoria and lack of concentration	N/c.167T>C

Table 1: Showed the constellation of the skeletal deformities and early manifestations of dementia.

Results

The clinical and the radiographic phenotypic characterizations, plus the natural history of the disease regarding the neurological and the osteogenic outcomes are almost compatible with the genotype of Nasu-Hakola syndrome. Family history represented two sisters (one half and one full biological sisters) also with a history of fractures, parents and grandparents all showed a history of fractures and early dementia. Whole exome sequencing revealed heterozygous missense mutations in TYROBP gene encoding for a cell-surface adaptor protein, which is part of a signaling complex triggering activation of immune responses (Fig. 3).

Female Patient with Nasu-Hakola Disease

A-42-year-old-unrelated female patient was referred because early life tarsal bone fractures which was followed by carpal fractures. She received the diagnosis of idiopathic osteoporosis and was treated extensively with calcium supplements and anti-resorptive medications. Lately she developed persistent headache, lack of concentration, euphoria and dementia. The clinical and radiological phenotype were totally compatible with Nasu-Hakola syndrome (Fig. 3).

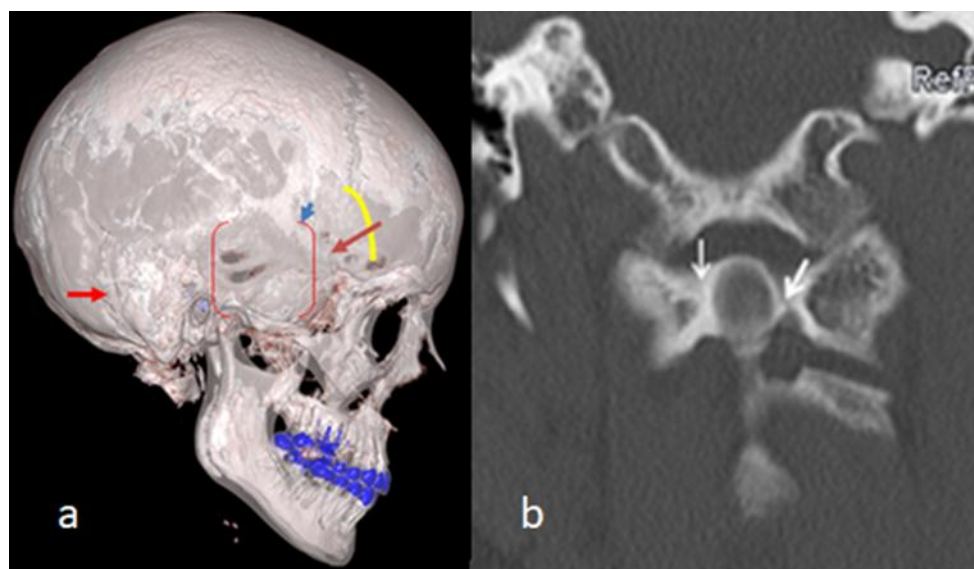


Figure 3: a,b: 3D reconstruction CT scan of the lateral view of the skull of a-42-year-old- unrelated female patient with the diagnosis of Nasu-Hakola disease consumed extensive amount of supplemental calcium showed sclerosis of the squamosal suture (red brackets), sclerosis of the sphenoparietal (blue arrow) and the sphenofrontal sutures (yellow bracket) leads to the development of bilateral narrowing of the skull. Sclerosis of the occipito-mastoid suture (red arrow). The sclerosed sutures turned the skull into a rigid ankylosed and hyper-calcified bone. A situation which might lead to skull dysplasia which prone to fractures. Observe the diffuse dysplasia of the rest of the skull bones which signifies high risk of minor trauma which can have a negative impact mortal/morbid on the middle meningeal artery (a). Coronal reformatted CT scan of the atlanto-axial joint (C1/2) of the same patient showed calcified horns like protrusions with diminution of the distance between the lateral mass of the atlas and the body of C2. Similar horn like protrusion along the atlanto-occipital joint-arrows-look like articular arthrosis. The overall pathology originated from ossification of the transverse and alar ligaments, which might lead to disturbed blood supply by the vertebral artery secondary to hyper-calcified vasculature (b).

Discussion

In patients with osteoporosis, the main reference for most of physicians is the Bone Mineral Density (BMD) measurement tools. The BMD has been applied blindly to the majority of patients with osteopenia and/or osteoporosis. Ignoring to interpret the associated clinical abnormalities and keep their eyes on just one symptom such as osteoporosis. This failing methodology made the epidemiology of osteoporosis in the literature skyrocket. Studies showed that more than one million patients in the United States alone are diagnosed with osteoporotic fractures annually [9].

The research efforts to understand the etiology of osteoporosis has been solely focused on studies of markers of bone formation (the osteoblast), as well as focusing on other markers such as alkaline phosphatase and osteocalcin. Though in some patients,

analyzing type I collagen has been applied [10,11]. This strategy has led to throwing hundreds of patients with osteoporosis in one basket. No other vital considerations have been applied to scrutinize the clinical/radiological phenotype of patients.

All our patients consumed large quantities of calcium supplements along with vitamin D3 over a period of almost a decade. For the index case of family I, we encountered substantial pathological deposition of calcium over the cranial bones (massive sclerosis of the facial bones and the cranial sutures turning the physiological flexible cranial sutures into a compact ankylosed /rigid structures). Ankylosed cranial sutures are highly susceptible for a serious cranial and intra-cranial complications. Minor trauma can lead to fatal hemorrhage of the middle meningeal artery. Furthermore, we observed extensive calcifications of the glabella, supraorbital foramina, and calcification of the greater wing of the sphenoid bone. Calcification of the sphenoid bone leads to obliteration of several blood vessels which conveys blood and nerves to the head and neck. In family II, dementia has been previously recorded in old age parents and grandparents. Surprisingly, the new generation of the index case started suffer from early dementia. We postulate that the early manifestations of dementia are strongly connected with the heavy administration of calcium. Excessive calcium intake may have dreadful results upon cerebral integrity [12-15]. Bostick, et al., studied 387 deaths within the Iowa Women's Health Study cohort. They concluded that a total calcium intake below 700 mg/day but not above 1400 mg/day was associated with higher mortality from ischemic heart disease. Surprisingly, other studies for re-analyses of randomized trials have confirmed a higher rate of both myocardial infarction and stroke by 25% to 30% and by 15% to 20%, strongly correlated to calcium supplements [16].

Conclusion

We wish to stress that our current study discussed two vital elements, firstly the etiological diagnosis which is based on genuine clinical documentation and secondly, the devastating relationship between the consumption of supplemental calcium, vitamin D and anti-resorptive medications in patients with ill-defined diagnosis. Finally, we wish to stress that, despite the improvement of the DEXA figures in accordance with the designed therapy. Unfortunately, they started to manifest a new set of serious pathological complications because of progressive ossification of the cranial bones and cerebral structures.

Conflict of Interest

The authors have no conflict of interest to declare.

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