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RESEARCH ARTICLE

UNUSUAL ASSOCIATION OF MENINGIOMA AND PITUITARY HYPOPLASIA IN A PATIENT WITH OSTEOGENESIS IMPERFECTA

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Abstract

Osteogenesis imperfecta (O.I.) is a rare inherited disorder that alters the physiological structure of connective tissue. In some cases, several neurological features have been described. We report.the case.of.a.10years old boy with a knownfamilyhistory of type I OI who suffered from repeated bone fractures, dorsal kyphoscoliosis, bone fragilityand severe stature weight growthdelay. The Brain MRI revealed pituitary hypoplasia, with a fortuitous discovery of a parietal plane meningioma. The association of osteogenesis imperfecta and meningioma, as well as osteogenesis imperfecta and pituitary hypoplasia, have rarely been reported in the literature; however, no accessible case of the association of the three entities has been described before within the limits of our research.The objective of our work is to demonstrate a possible pathophysiological link between these three entities.

Introduction:

Osteogenesis imperfecta, also known as “brittle bone disease” isarareconditioncharacterizedby bonefragility. Itsprevalenceisabout 6-7/100,000.(1). Thediseaseisinheritedinanautosomal dominantautosomalrecessiveorXlinkedrecessivemanner.The symptoms are mainly skeletal, however, in some cases of extra skeletal impairmentsthe nervous system can be affected; resulting in some severe neurological manifestations.

We report the case of a patient with osteogenesis imperfecta, parietal meningioma and GH deficiency secondary to pituitary hypoplasia.

Case Report:

A 20 years old male was admitted to our department. He has a history of several fractures (a total of 7) that occurred during his childhood, dorsal kyphoscoliosis, and diffuse bone demineralization. The diagnosis of OI was established at the age of 10. The patient received surgical treatment for his right femur fracture, an orthopedic treatment for his other fractures was provided.

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A detailed analysis of his biometric data at the age of 12 revealed a severe stature weight growth delay (height: -4SD, weight: -4SD) in an impubescent patient,with bone age3 years below chronological references, hormonal explorations revealed a somatotropic deficit without impairment of other endocrine axes (IGF1: 75 nmol/l, with absence of stimulation on insulin hypoglycemia test and levodopa test). Hypothalamic-pituitary MRI revealed hypoplasia of the anterior pituitary gland**(Image 1)**, andthefortuitousdiscovery of a right parietal plane meningioma8 mm thick and 35 mm long, with no mass effect**(Image 2)**.
The patient did not undergo any surgical treatment nor radiotherapy for his meningioma, a simple clinical and radiological monitoring was recommended, with follow-up indicating volumetric stability of this benign tumor. 8 years after the patient has reached puberty with Tanner stage 5 testicles, penis size >2DS, despite the absenceof replacement therapy with recombinant GH,the results of hisgrowth curve monitoring showed a remarkableamelioration regarding his staturereaching -2 SD, no weight gain has beennoted.

Regarding his osteogenesis imperfecta, the patient did not benefit from any drug treatment (bisphosphonate) but simply underwent clinical/radiological monitoring (cobb angle).
Family investigations revealed that his younger brother had a stature weight growth delay without somatotropic deficiency, and bone lesions associated with osteogenesis imperfecta.

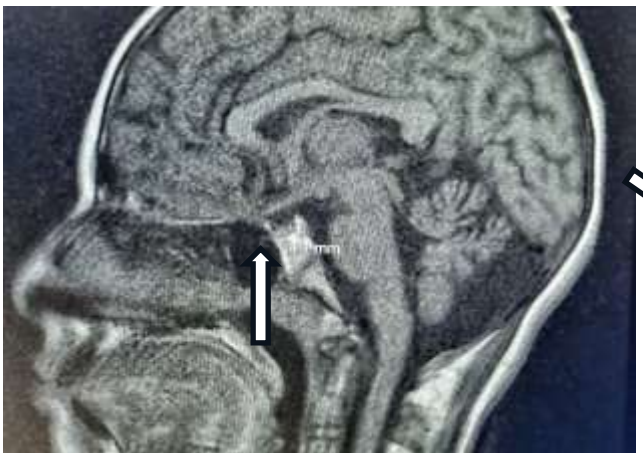

Image 1:sagittal section of our patient's MRI showing a hypoplastic pituitary gland

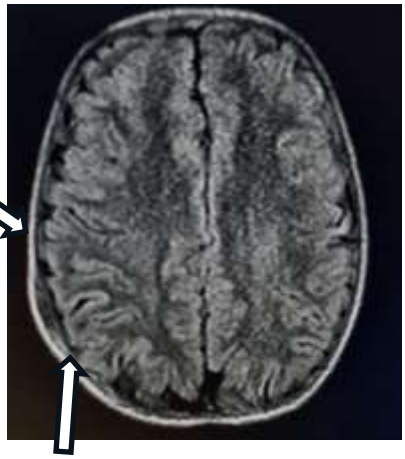

Image 2: Cross-section of our patient's MRI showing a right parietal plane meningioma

Discussion:

As reported above in our observation, we are discussing the association in the same patient of osteogenesis imperfecta meningioma and pituitary hypoplasia, is it an accidental association or a well-defined syndrome that has already been reported in the literature, involving several therapeutic difficulties?

Osteogenesis imperfecta is a group of genetic diseases mainly characterized by the occurrence of multiple bone fractures as a result of a congenital bone fragility.

AlterationsinatleastgeneshavebeenassociatedwithOI.MutationsinCOL1A1orCOL1A2, whichcodeforthepro-alpha1orpro-alpha2chainoftypeIcollagen, accountforover85%of pathogenicvariants, resultingin a mixture of normal and abnormal collagen. A positive mutation in type I collagen confirms the diagnosis. In some cases, the diagnosis can be established clinically in patients with a positive family history of OI with associated clinical features. (1)

The presence of type I collagen fibers in many structures other than bone (organ capsules, fascia, cornea, sclera, tendons, meninges and dermis), results in the presence of variable extra-skeletal manifestations: blue sclera, short stature, dentinogenesis imperfecta, hearing disorders, hyperlaxity of ligaments and skin [2].
In our case, the diagnosis of OI was based on clinical criteria: multiple fractures mainly regarding the long bones, dorsal kyphoscoliosis, stature growth delay with a brother suffering from OI. A meningioma was also discovered

incidentally.
The association of OI and meningioma is rarely reported in the literature, and raises the question of the pathophysiological mechanism of this coexistence [2].

A possible generalized disorganization of type I collagen could explain the association of OI and meningioma, since this type of collagen is notedly abundant in meninges, which could lead to the development of tumors.

Several chromosomal abnormalities have been implicated in meningioma formation, but they do not appear to be linked to OI pathogenesis. No genetic correlation has yet been established between meningioma and OI. [2]
OI may be associated with stature growth delay, but in our case the severity of the delay (height: <4DS, weight: <4DS) prompted a thorough investigation to explore its origin, the results showed a somatotropic deficit on 2 stimulation tests as well as a pituitary hypoplasia that appeared on MRI.
GH deficiency associated with OI can be explained by two hypotheses:
-Genetic: the association of mutations in 2 genes was described in 2020 in a Thai boy whose genetic investigation revealed a heterozygous de novo mutation in the COL1A2 geneaswellasa heterozygous missensemutation, c.364C>T.(p.R122W)ontheLHX4gene, inheritedfromhishealthyfather LHX4 p.R122Wthuslosesitsabilitytoactivate*POU1F1*, *GH1*, validatingitspathogenicity,whichexplains theGHdeficiencyfoundinthispatient. BrainMRIshowedhypoplasiaofthepituitarygland. [1]
-Anatomical: OI may be accompanied by a flattening of the bones at the base of the skull known as platybasia, which causes a compression ofthe components of the basal side of the cranium: the brainstem, cerebellum and cranial nerves, leading to basilar invagination, responsible for headaches, nystagmus, ataxia, impaction of cranial nerves, or pituitary hypoplasia. [3]**(Image 3)**

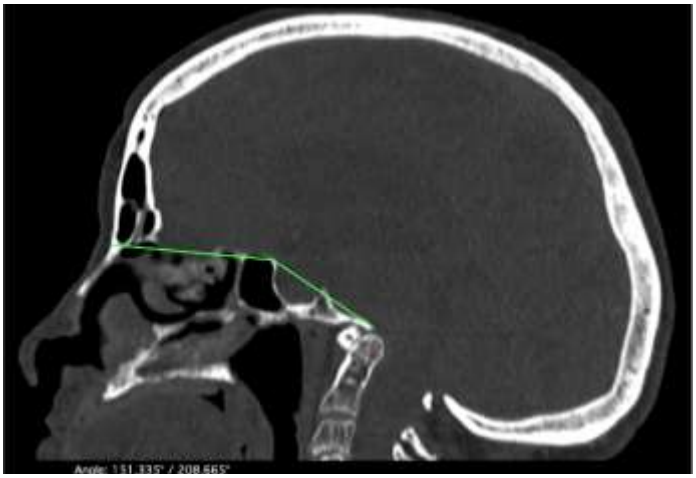

Image 3: Sagittal section of a brain scan with a marked basal angle of 151°[3].

Therapeutic management of osteogenesis imperfecta varies according to disease severity, age and functional status. Treatment can range from simple restrictions such as avoiding contact sports, to orthopedic or even surgical interventions and rehabilitation. The treatment aims to maximize mobility and competence, and reduce pain and bone fragility. Bisphosphonates represents an important advance in treatment, as they increase bone mineral density and reduce the risk of vertebral fractures. Vitamin D also plays an important role in reducing the risk of fractures. [3]. The treatment of progressive scoliosis consists of wearing an orthopedic corset.
Our patient underwent orthopedic treatment for the majority of fractures, and surgical treatment for his femoral fracture, with therapeutic education, his scoliosis was not progressive. We also recommended vitaminocalcium and bisphosphonate treatment before referring the patient to rheumatologists.

In case of somatotropic insufficiency, treatment with growth hormone can't be considered, due to several contraindications: unoperated parietal meningioma and osteogenesis imperfecta complicated by dorsal kyphoscoliosis.

The result of Yun et al study regarding kyphoscoliosissuggest that Cobb angle increased by 1 degree per year in patients treated with GH, whereas there was no significant annual change in the control group. Parc et al reported

that the rate of scoliosis progression was 16.4% during GH treatment and that the Cobb angle increased significantly by about 4 degrees from baseline during an average of 5.5 months of GH treatment. [4,5]

As for meningiomas who express GH receptors, in vitro activation of the GH/IGF-1 axis increases meningioma growth rates. In vivo model, down-regulation of the GH/IGF-1 axis reduced meningioma growth [6]. GH treatment could induce cell proliferation, especially if the patient has been treated with radiotherapy. The potential risks of aggravating or accelerating the progression of these cancers must be weighed against the benefits of GH treatment. [7]

The treatment of the meningioma is not always surgical; a careful clinical monitoring with neurological follow-up and periodic MRI is reasonable for asymptomatic patients with a small meningioma without oedema. The first MRI should be performed 6 months after the first scan, and then every year thereafter. After the age of 5, MRI must be performed every 2 years.[8]
A simple monitoring of our patient's meningioma was recommended, given its asymptomatic nature, size and location.

In the light of the challenges that our patient presented, a multidisciplinary team meeting was held to discuss the eventualities regarding his treatment, as a result, our approach consisted on a simple follow-up of the of auxiological and radiological criteria. Despite the absence of replacement therapy with recombinant GH, monitoring of the growth curve shows a stature catch-up of 2 deviations without any weight gain, this could be explained by the pubertal growth peak.

Conclusion:

The unusual association of OI, meningioma and pituitary hypoplasia should highlight a potential etiopathogenic link between these 3 entities, the treatment with GH in our case was a real therapeutic challenge with a risk of scoliotic and meningioma progression.

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