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Frontal behavior dysfunctions revealing a dramatic progression of complex cranial base abnormalities in a severe osteogenesis imperfecta.

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Nothing to disclose

BACKGROUND

In our bone unit, we were following since their younger age, two brothers with a severe neonatal osteogenesis imperfecta. The severity of the disease combined with unaffected consanguine Turkish parents argued for a recessive autosomal transmission. Both presented with highly severe form of osteogenesis imperfect (OI): repeated vertebral and peripheral fractures, long bone deformations, chest deformation with cyphoscolisois, centromedullary nails on the lower limbs, major motor handicap and disability (wheelchair), and growth retardation below – 2 standard deviation score.

METHODS AND NVESTIGATIONS

The younger boy had received treatment with bisphosphonates since the first year of life, associated with vitamin D and calcium supplementation, and with intensive physical rehabilitation. At fourteen years old, bisphosphonates reached their limits: repeated untraumatic fractures, delayed fracture healing, osteosynthesis material loosening. He had hypocaloric intake and denutrition. A gastrostomy was performed. We confirmed a growth hormone deficiency. The cerebral MRI showed pituitary hypoplasia and asymptomatic craniocervical junction abnormalities. Basilar impression was associated to clivus malposition and brainstem deformation. The medullar MRI showed known vertebral fractures and scoliosis. We stopped bisphosphonates and started nocturnal enteral nutrition and growth hormone treatment in order to improve bone mass and strength.

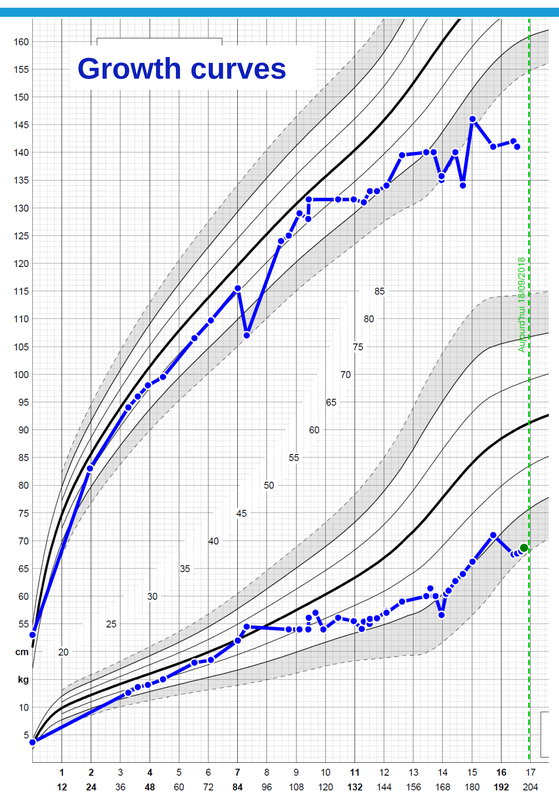
EVOLUTION AND MANAGEMENT

During 2 years, no fracture occurred. Nutritional status was better. At the age of sixteen years old, he presented behavioral troubles: disinhibition, motor instability, stereotypies, sphincter dysfunctions. Neurological examination was normal, especially without headache, or visual impairment, no sign of cranial hypertension, or pyramidal syndrome. However ophthalmologic examination revealed papilledema.

TDM survey: The cerebral TDM showed an important triventricular hydrocephalia and basilar impression.

Treatment: We stopped growth hormone treatment. A ventriculostomy was performed. Surgery was well tolerated and improved the frontal behavior. Three months after surgery, we began Zoledronic acid infusions.

Genetic testing confirmed a very rare autosomal recessive OI. The two brothers presented a homozygous mutation in FKBP10 gene: c.831dupC, p.(Gly278ArgfsTer95). That gene encodes FKBP65, a chaperone protein that participates in type I collagen synthesis and folding. Mutation in that gene is involved in OI type XI with progressive deforming bones [1]. Bisphosphonates may improve bone mass in that recessive form [2]. The younger boy, with the most severe evolution, presented also an association with two homozygous variants in LEPRE1 (leucine-and –proline-enriched proteoglycan 1) gene: c.194G>A, p.(Arg65Gln) and c.1795G>A, p.(Val599Met). That gene encodes for P3H1 (prolyl 3-hydroxylase1) that is involved in post-translational modifications of collagen



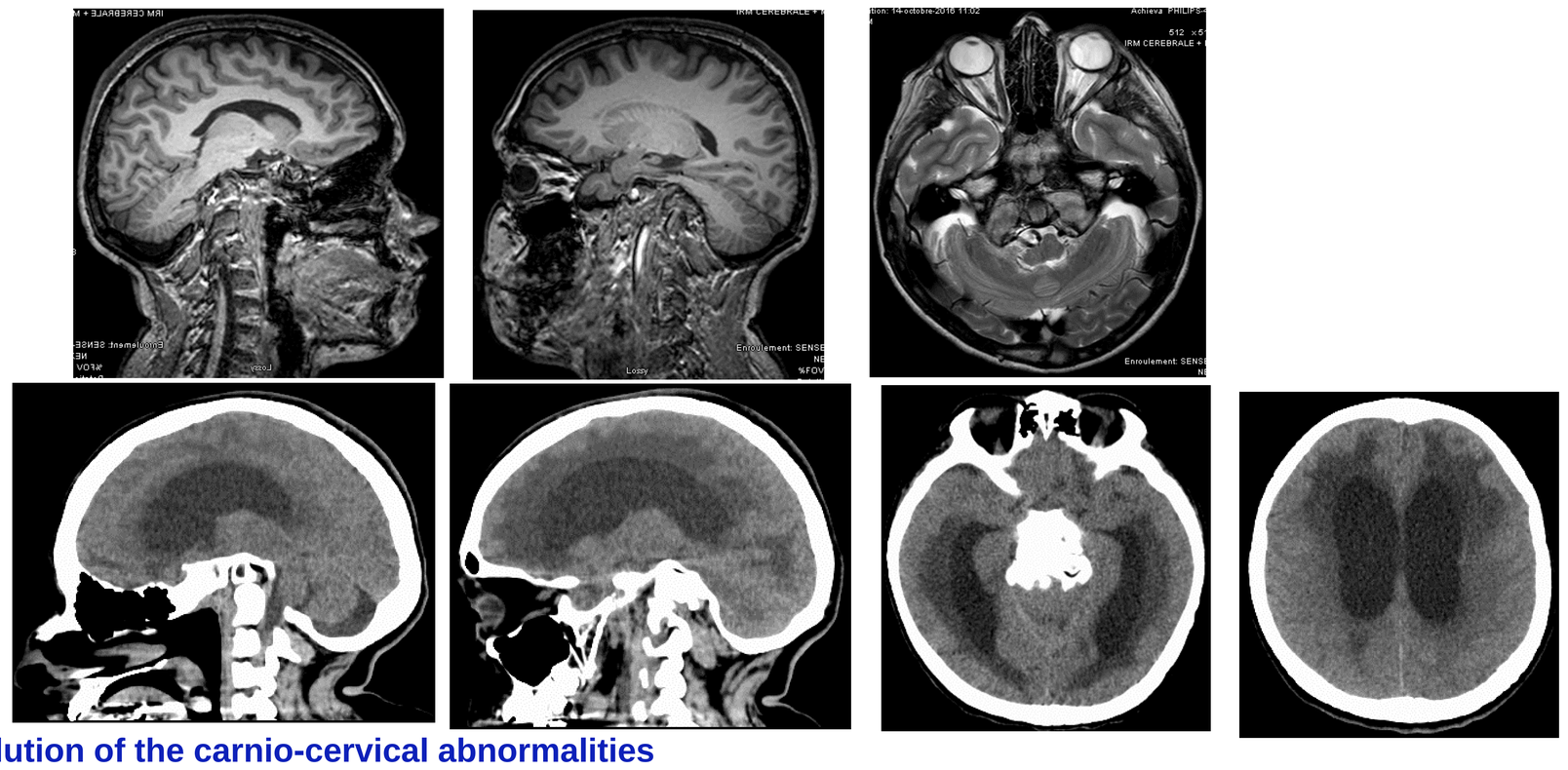


Fig1 – Evolution of the carnio-cervical abnormalities

CONCLUSION

In that family, with homozygous mutation in FKBP10 gene, the phenotype concerning the cranial base is different. While treated earlier with bisphosphonates infusions, the younger boy had a worst evolution curse and more complex cranial abnormalities. Usually phenotype is the same in the same family. The younger boy presents superimposed variants in LEPRE1 gene that can affect the more severe evolution. Genetic testing is usefull in severe forms of OI for treatment options and for understanding unusual complications. Neurological examination and behavioral evaluation are essential in severe OI. Ophtalmologic examination and cerebral imaging must be performed in frontal behavior dysfunction.

BIBLIOGRAPHY

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