Mutation in the TBCE Gene associated with Kenny-Caffey type 1 syndrome:A rare cause of hypocalcemia

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I-Background:

Kenny-Caffey syndrome type 1 is a rare autosomal recessive syndrome caused by mutation in the TBCE gene (Tubulin specific chaperone E) located in the chromosome region 1q42-q43;TBCE is required for α and β tubulin dimerization and microtubules polymerization. Less than 60 cases have been reported in the literature especially in the Middle East and Arabic countries.[1,2]
This syndrome is characterized by growth retardation, dysmorphic features, with thickened bone cortex and medullar stenosis, hypocalcemia with hypoparathyroidism, teeth anomalies. Hypopituitarism with pituitary hypoplasia may be associated .[2]

II-Case report:

A three years old Algerian girl was referred to pediatric endocrinology unit for etiological research of **hypocalcemia.** Her birth weight was **1370g** .At the 72 hour of birth she has been admitted in intensive unit for hypocalcemia which has been related to prematurity. At 13 months she developed multifocal seizures and hypocalcemia was detected with total calcium 6,8mg/dl , serum parathormone (PTH) level was low :2,8ng/ml. She has been treated with calcium and vitamin D.

On examination:she has **severe growth retardation** weight was 6Kg(<-3DS), normal mentality, height 65cm (<-3DS) ,**dysmorphic face** with microcephaly, deep-set eyes with hypermetropia ,peaked nose, thin lips, micrognathia, low set ears ,depressed nasal bridge, microdontia ,enamel defects and caries (picture 1).

Biologic investigations:
Calcium: 2,38mmol/l (under calcium and vitamine D supplements)
IGF1:8,3ng/ml[low for age]
Glucagon test shoed **low GH secretion** with pic of 5,23 mUI/l. [<20mUI/l]
Insulin test: not done (weight<10kg)
FT4:13,5pg/ml[6,35-18,9],TSH:4µU/mL [0,3-4].
Cortisol:267nmol/l[131-642] .ACTH:29pg/ml [<60]
Prolactin:8.9ng/ml[normal for age]

Radiological findings:showed **Internal cortical thickening** and medullary stenosis of the tubular bones(picture 2) .
Pituitary MIR: showed **pituitary hypoplasia** (1,5mm).

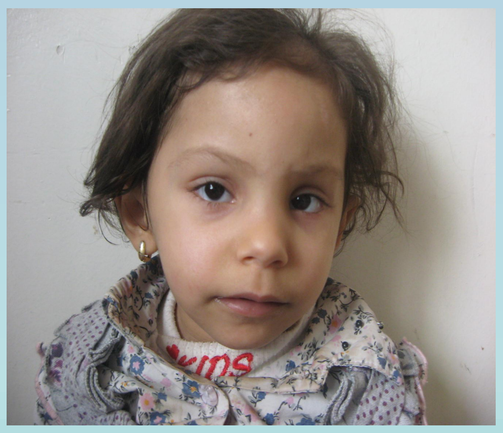
Regarding the association IUGR, short stature ,dysmorphic features, ophthalmologic abnormalities ,dental anomalies and hypoparathyroidism ,**Kenny-Caffey** syndrome has been evocated and confirmed genetically: Variant **c.155_166del in the TCBE** gene has been identified in **homozygosity** ,which is predicted to cause at protein level, an in frame shift deletion of four amino acids **(p.ser52_gly55del)**which is compatible with the clinical diagnosis of Kenny-Caffey syndrome.

III-Discussion:

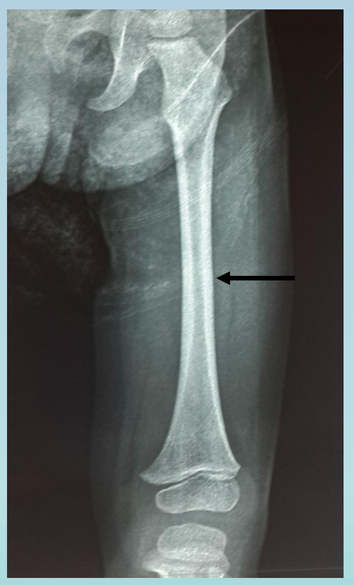
Kenny-Caffey syndrome (KCS) is a rare osteosclerotic bone dysplasia characterized by hypocalcemia,short stature, ophthalmological features, and teeth anomalies. **The TBCE gene** that encodes a molecular chaperone required for **heterodimerization of α and β tubulin** .Microtubules are essential for cellular processes (cell division, intracellular transport and motility)[1-3]

Sanjad-Sakati syndrome or HRD(Hypoparathyroidism-Retardation-Dysmorphism) have the same phenotype with different locus name.[4]

TBCE and microtubules may play crucial role in the development of **parathyroid gland** .**GHI** has been reported in cases with **KCS/HRD** syndromes with the same related mutation ,and it is possible that the pituitary hypoplasia is due to the **defective hypothalamic –neuroendocrine regulation inducing reduction of releasing hormones** [2-4]. In an Israeli cohort, a 15-yr follow-up of children with HRD syndrome demonstrated poor catch growth up during infancy .The authors suggested that mutation in the TBCE affected **microtubule assembly and chondrocytes maturation** .[5]



Picture 1



Picture 2

VI-Conclusion:

Kenny-Caffey syndrome is a rare cause of hypocalcemia .The association of severe short stature ,dysmorphic face ,teeth abnormalities and bone dysplasia must guide us to suggest the diagnosis especially in the Middle Eastern and Arabic countries and confirm them genetically. Pituitary functions should be evaluated because of possible association of hormonal deficiency.

V-Bibliography:

1-Youssra Moussaid et al. European Journal of Medical Genetics 55 (2012) 441e445
2-Raja Padidela et al. J Clin Endocrinol Metab, August 2009, 94(8):2686–2691
3-*Ruti Parvari et al.* nature genetics • volume 32 • November 2002
4- Ahhmad et al.J Med Genet 2000;37:145
5-Hershkovits et al.Pediatr Res 62:505-509