Neonatal Hyperparathyroidism with Homozygous Missense Mutation in the CASR Gene

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Introduction

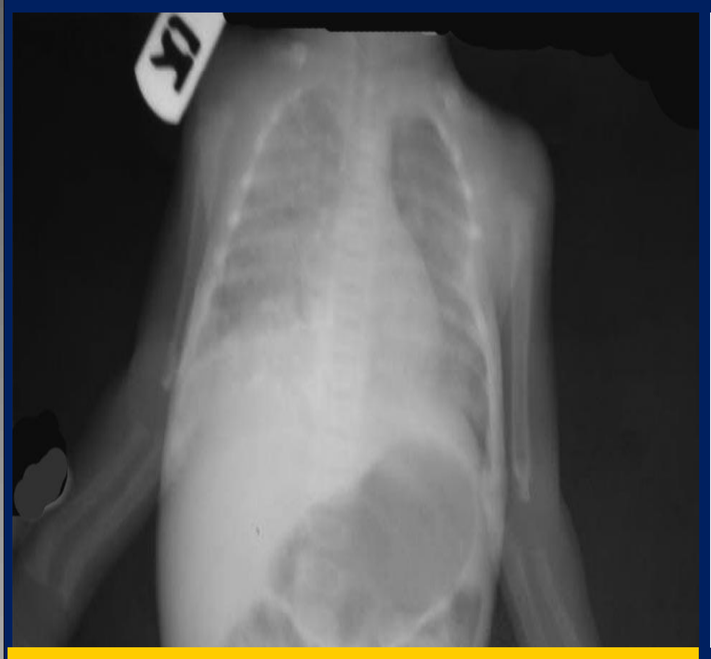
Neonatal severe hyperparathyroidism is a rare disorder , caused by in activation mutation of the CASR gene. (1,2) . These receptors expressed in parathyroid glands , renal cells ,bone and thyroid glands . These receptors regulate and maintain calcium hemostasis.

Heterozygous loss of function in CASR give rise to familial (benign) hypocalciuric hypercalcemia in which the life long hypercalcemia is generally asymptomatic.

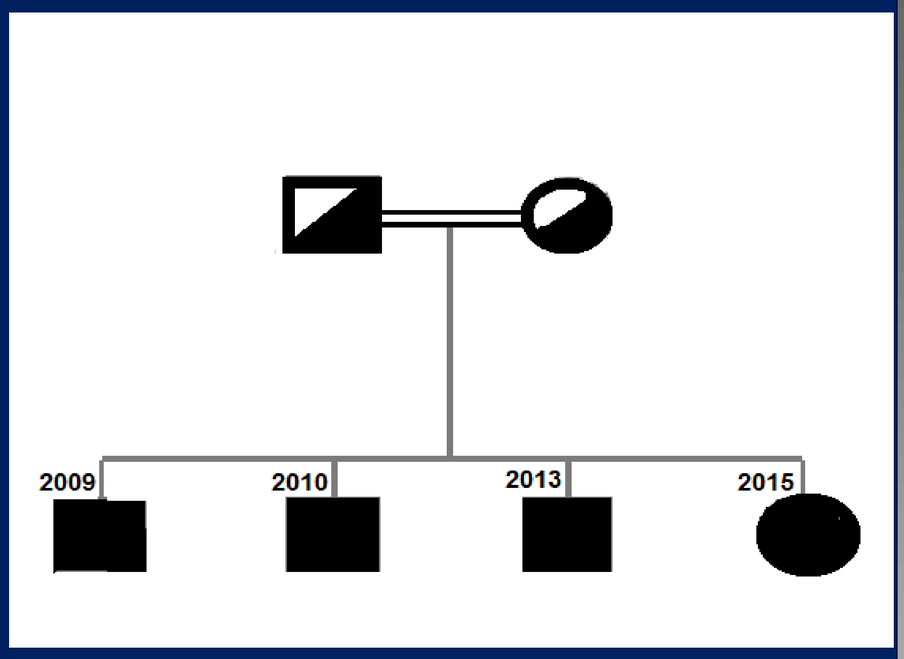
Familial hypercalcuric hypercalcemia (FHH) patients demonstrates inappropriately normal serum concentration of PTH despite hypercalcemia . Homozygous mutation in CaSR gene manifested as neonatal severe hyperparathyroidism in the first few weeks of life "3" which characterized by severe hypercalcemia and bony demineralization in infancy, those infants exhibit polyuria, dehydration and hypotonia associated with a history of failure to thrive, irritability ,constipation and delayed neuropsychological development. Parathyroidectomy is the main stay of treatment (4).

METHODS

Consent was obtained from one Libyan family with neonatal sever hyperparathyroidism with four affected siblings to perform familial genetic analysis ,where clinical and biochemical data for parents and their siblings were collected , skeletal survey of affected siblings was interpreted and out comes after parathyroidectomy was evaluated



- Skeletal survey of patient, demonstrating
- Multiple fractures and generalized steopenia



Pedigree of the affected family

RESULTS

Individual	Calcium	PTH	Gene	Clinical	Intervention
F	12mg/dl	70 pmol/l	Heterozygote mutation (p.Arg680His;CGC>CAC)in exon 7 des CaSR Gens	Carrier	Asymptomatic
M	9mg/dl	60pmol/l	Heterozygouste mutation P(Arg 689 His, CGC>CAC in exon 7 desCASR	Carrier	Asymptomatic
1 ♂	?	?	?	Died at 3 wks.	-------
2 ♀ PROBAND	18mg/d l	1118 pmol/l	Homozygous mutation P(Arg 689 His, CGC>CAC in exon 7 des CASR	Died at 3yr	Pamidrunate & Parathyroidecomy
3 ♂	20mg/dl	1501 pmol/l	Homozygous mutation P(Arg 689 His, CGC>CAC in exon 7 des CASR	Alive	Pamidrunate & Cincalcet Parathyroidecomy (at 1yr)
4 ♂	28mg/dl	1221 pmol/l	Homozygous mutation P(Arg 689 His, CGC>CAC in exon 7 des CASR	Alive	Pamidrunate & CFincalcet Parathyroidecomy (8wks)

CONCLUSIONS

- NSHPT is a rare disease due to CASR gene mutation in homozygous state that requires a high index of suspicion and a very good history to make an early diagnosis and avoid complication. Genetic counseling for a family who have an affected sibling with CASR gene mutation .
- Medical treatment is helpful in stabilizing the patient and bridging him to definitive surgical treatment, Cincalcet may work in some mutations not all.
- Parathyroidectomy with auto-transplant on half a gland in the forearm remains the most effective intervention that associated with long term calcium level stabilization.

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