Lack of Cinacalcet Response in Neonatal Severe Hyperparathyroidism due to Homozygous CASR Mutation

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INTRODUCTION

- Neonatal severe hyperparathyroidism (NSHPT) is a rare disorder caused by inactivating calcium-sensing receptor (*CASR*) mutation.
- The calcium sensing receptor(CASR) is the key sensor for extracellular calcium. Inactivating mutations of CASR elevate the set point of receptor activation by extracellular calcium.

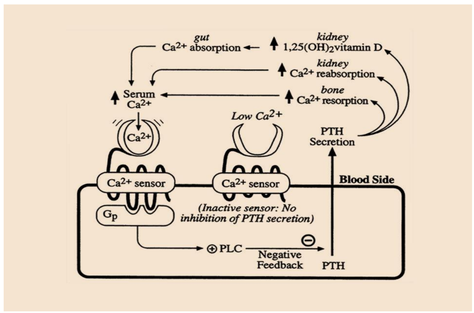

Figure-1 *Showing calcium homeostasis by Calcium sensing receptor (CASR)*

AIM

- To determine the clinical spectrum of NSHPT due to *CASR* mutation.

METHOD

- Retrospective review of NSHPT cases due to *CASR* mutation at a Tertiary Care Hospital in Lahore in last one year.

RESULTS

Presentation

- Total 3 cases (2 females) from three different families of NSHPT due to *CASR* mutation were identified.
- All born to consanguineous parents, with history of unexplained sibling death in case 1 and still birth in case 2.
- 2 cases were born IUGR and presented in neonatal age group with complains of lethargy, reluctance to feed and polyuria.
- 1 case presented at 4 months of age with nephrocalcinosis

Figure-2. Showing Underlying CASR mutations variants

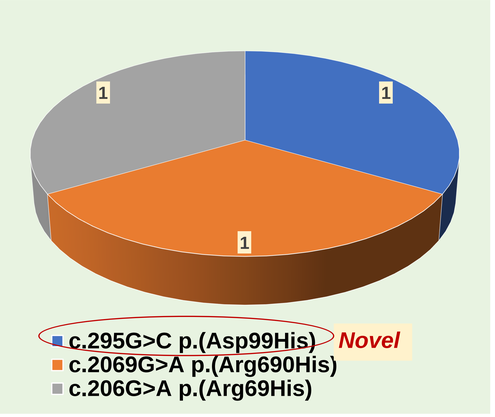

Table-1. Bone profile at presentation

Bone Profile	Mean	Range
Calcium (mg/dl)	21.5	20.4 – 23.1
Magnesium (mg/dl)	2.36	2.3 – 2.4
Phosphate (mg/dl)	1.7	1.2 – 2.2
Alk. Phosphatase (IU/l)	456	426 - 504
PTH (pg/ml)	900	642 – 1077
25-OH vitamin D (ng/ml)	18.5	16.7 -20.9
Urine calcium to creatinine ratio	0.4	0.4-0.5

hypercalcaemia, hypophosphatemia, raised PTH

Table-2 showing characteristics of different variants of *CASR* mutation

Characteristics	Case 1	Case 2	Case 3
CASR variant	c.295G>C p.(Asp99His	c.2069G>A p.(Arg690His)	c.206G>A p.(Arg69His)
Age of Manifestation (days)	25	120	20
Birth weight (Kg)	1.8	2.4	1.0
Calcium at presentation (mg/dl)	20.4	23.1	21.2
Phosphate at presentation (mg/dl)	2.2	1.8	1.2
Hyperhydration & Pamidronate	yes	yes	yes
Cinacalcet max dose (mg/kg/day)	3	3	3
Post cinacalcet Calcium (mg/dl)	18	17.2	16.6
Parathyroidectomy	yes	yes	No*

* Case 3 had a sad demise before surgery due to hospital acquired infection

Table-3. Post Parathyroidectomy outcomes

Post - parathyroidectomy	Case 1	Case 2
Age of parathyroidectomy (months)	2	6
Post-op Calcium (mg/dl)	9.1	9.2
Post-op Phosphate (mg/dl)	3.4	3.0
Post-op PTH (pg/ml)	3.5	<4.0

Figure-3 showing Case-1 undergoing Parathyroidectomy

CONCLUSION

- We have identified 3 cases of NSHPT due to *CASR* mutation
- None of our cases responded to cinacalcet and two of the cases ended up in parathyroidectomy.
- Efficacy of cinacalcet in NSHPT due to CASR mutation needs further randomized controlled trials
- There is need for studies with larger data to look for genotype and phenotype correlation.

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