Clinical Spectrum of Hypomagnesemia type 1 (HOMG1) due to Novel *TRPM6* mutation variants

P1-017

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INTRODUCTION

- **Hypomagnesemia type 1 (HOMG1) is a rare autosomal recessive condition due to inactivating *TRPM6* mutation.**
- **Inactivating *TRPM6* mutation results in selective intestinal defect in transcellular absorption of Mg (figure 1) leading to impaired PTH secretion and responsiveness with consequent secondary hypocalcaemia.**

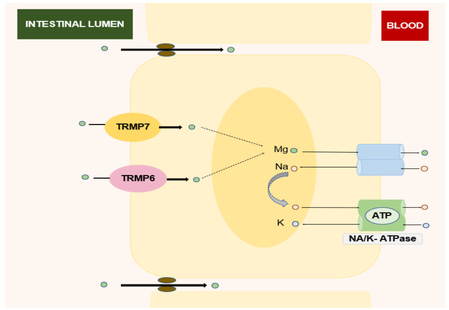

Figure-1 *Showing paracellular (passive) and transcellular (TRPM6/TRPM7 mediated) intestinal Mg absorption*

AIM

- **To determine the clinical spectrum of HOMG1 due to *TRPM6* mutation.**

METHOD

- **Retrospective review of HOMG1 cases due to *TRPM6* mutation at two specialist paediatric endocrine centre in Lahore over last two years.**

RESULTS

- **Total 7 cases (all male) from six different families of HOMG1 due to *TRPM6* mutation were identified.**
- **All born to consanguineous parents, with 5/7(4 families) having a history of sibling death due to seizures.**
- **Irritability and excessive cry was first symptom appeared at 22 (9-30)days followed by generalized tonic colonic seizures at 2.2 (1.5 - 3) months.**
- **Six cases presented at tertiary care around 3-6 months and one at the age of 3 years.**

Figure-2. Underlying *TRPM6* Mutations variants

All cases carries homozygous mutation in *TRPM6* gene (4 different variant identified)

- **c.2538G>T p.((=))** — **n=4** — *No amino acid change. Substitution is near the highly conserve donor splice site*
- **c.3514C>T p.(Arg1172*)** — **n=1** — *Premature stop codon*
- **c.2162C>G p.(Ser721*)** — **n=1** — *Premature stop codon*
- **c.1420C>T p.(Arg474*)** — **n=1** — *Premature stop codon*

Novel mutation

Table-1 Bone profile at presentation

Bone Profile	Mean	Range
Magnesium (mg/dl)	0.7	0.4 – 1.1
Calcium (mg/dl)	6.7	5.2 – 8.1
Phosphate (mg/dl)	5.5	5.2 - 6.8
Alkaline Phosphatase (IU/l)	314	187 - 487
PTH (pg/ml)	18	16 – 20.6
25-OH vitamin D (ng/ml)	50.7	25 -120
Urine calcium to creatinine ratio	0.06	0.001 – 0.15
Fractional Excretion of Mg (Femg)	1.7	1.05 -1.9 %

Hypocalcaemia, hypomagnesemia, low/normal PTH, decreased FEMg

Table-2. Characteristics of different variants of *TRPM6* mutation

Cases	TRPM6 variant	Age of Manifestation Irritability, Excessive cry (days)	Age of Seizures (months)	Age of Diagnosis (months)	Initial serum Mg (mg/dl)	Initial serum Ca (mg/dl)	Oral Mg mg/kg/d	Serum Mg under therapy (mg/dl)	Side affects of Mg	Fits controlled
Case 1	c.2538G>T p.((=))	9	2	36	1	6.9	280	1.4	No	Yes
Case 2	c.2538G>T p.((=))	15	2	2	0.5	8.1	352	1.7	No	Yes
Case 3	c.2538G>T p.((=))	15	3	9	1.1	6.4	240	1.6	No	Yes
Case 4	c.2538G>T p.((=))	15	1.5	2	0.4	5.2	320	1.6	No	Yes
Case 5	c.1420C>T p.(Arg474*)	45	3	3	1.1	6.2	400	1.5	Yes *vomiting*	Subtle *levetiracetam*
Case 6	c.3514C>T p.(Arg1172*)	30	3	6	0.5	8.1	360	1.9	Yes *vomiting*	Yes
Case 7	c.2162C>G p.(Ser721*)	30	1.5	4	0.3	6.3	400	2	No	Subtle *levetiracetam*

Inference

- c.2538G>T p.((=)) is the most common variant (n=4). It seems to be manifested at the mean age 13.5 days and responded to oral Mg mean dose of 298 mg/kg/d with good control of seizures (all cases off antiepileptics).
- Other variants manifested at mean age 35 days and responded to slightly higher oral Mg (mean 386 mg/kg/day). 2/3 of them were still on antiepileptics despite normal serum Ca and Mg.

CONCLUSION

- **We have identified 7 cases of *TRPM6* mutation with 4 different variants (3 are novel mutations).**
- **c.2538G>T p.((=)) is the most common variant (n=4). It seems to be manifested in early neonatal age and responded to lower oral dose oral Mg with good control of seizures as compared to other variants (premature stop codon).**
- **There is need for studies with larger data to look for genotype and phenotype correlation.**

REFERENCES

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