**Long term management of a family with Calcium –sensing receptor mutation**

**Background**

Release of parathyroid hormone is regulated mainly by extra-cellular calcium ion concentration which is sensed by calcium-sensing receptors (CaSR) on surface of parathyroid cells. Activating or inactivating mutations in the CaSR produce altered extracellular calcium sensing and, therefore, inappropriate PTH release with respect to the prevailing serum calcium concentration. Both genetic and acquired disorders of calcium sensing receptors are known.

Activating mutations in the calcium-sensing receptor gene *CASR* cause autosomal dominant hypocalcaemia. Here the set point for extra-cellular sensing of calcium is lowered, leading to a suppressed PTH and hypercalciuria even in the context of low serum calcium levels. Hypomagnesaemia may also occur.

The syndrome needs to be recognised and distinguished from hypoparathyroidism as overzealous calcium and vitamin D replacement leads to clinically significant hypercalciuria, nephrocalcinosis and renal impairment. Therefore, finding of hypocalcemia that is not associated with an un-detectable or very low serum parathyroid hormone concentration and markedly reduced urinary calcium excretion should suggest a diagnosis of hypocalcemic hypercalciuria, which can be confirmed by analysis of mutations in the calcium-sensing–receptor gene.

**Case report**

We are aware of a four generation family with an activating mutation in *CASR* (c.354C>A; p.Asn118Lys) leading to an autosomal dominant hypocalcaemia phenotype. Here we compare and contrast clinical features of 3 family members (mother (A) and two daughters (B and C)) who have been managed with this condition.

Family member A is 52 years of age and biochemically has hypocalcaemia, hypercalciuria and hypomagnesaemia, with a suppressed PTH. She has a documented decline in eGFR from 45 to 23 mls/min/1.73m2 in the last 8 years with ultrasound evidence of bilateral medullary nephrocalcinosis. Treatment for symptomatic hypocalcaemia has included 1-alpha-calcidol. Family member B, aged 29 years, has a similar biochemical picture, again with nephrocalcinosis and renal impairment, with an eGFR of 31 mls/min/1.73m2, deceased from 60 over the last 7 year. She has previously been treated with both calcium supplementation and vitamin D but this has now been discontinued. Family member C (daughter of A, sibling of B), aged 27 has a similar biochemical picture but preserved renal function and has been maintained, to date, off all calcium and vitamin D supplements. Despite this, however, she does have significant bilateral medullary nephrocalcinosis.

**Conclusions**

Despite all affected members of this family having a confirmed genetic diagnosis of *CASR* activating mutation, the clinical phenotypes and progression of renal impairment seems to have been influenced by use of both calcium and vitamin D supplementation. Caution must be used in the use of agents to correct serum calcium in patients with this condition as these may result in progressive renal impairment secondary to nephrocalcinosis.