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Characteristics Of Adults with Autosomal Dominant Hypocalcemia Type 1 (ADH1) Enrolled In The CLARIFY Disease Monitoring Study

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Autosomal dominant hypocalcemia type 1 (ADH1), caused by gain-of-function calcium-sensing receptor gene (*CASR*) variants, is characterized by low parathyroid hormone (PTH) concentrations, hypocalcemia, hypercalciuria, hyperphosphatemia and hypomagnesemia. While a rare disease, ADH1 is one of the more frequently identified causes of genetic hypoparathyroidism. Conventional therapy includes calcium (Ca) and/or active vitamin D, but this regimen incompletely corrects the hypocalcemia and is associated with persistent hypercalciuria, which may result in renal complications including nephrocalcinosis (NC), nephrolithiasis (NL), and chronic kidney disease (CKD). The CLARIFY disease monitoring study [NCT05227287] is a global, multicenter, longitudinal study to understand disease burden, management, and progression in children and adults with ADH1 over a 5-year period. Here we report data on the characteristics of adult participants at study entry. As of November 2023, 45 adults (≥18 years) with ADH1 were enrolled, with a mean±SD age of 42.1±16.5 years (range 18-80). The mean±SD age of a hypocalcemia diagnosis was 19.1±19.1 years, while the mean ±SD age for a diagnosis of ADH1 was 28.2±20.6 years. As reported on medical history, in decreasing order of prevalence, 36% (16) had NC, 22% (10) had intracranial calcifications, 11% (5) had history of seizures, 11% (5) had CKD, 9% (4) had cataracts, 7% (3) had NL, and 4% (2) had undergone renal transplant. Treatment data were available for 43 participants and included the following: 74% (32) Ca and active vitamin D, 9% (4) Ca alone, 9% (4) active vitamin D alone, 37% (16) magnesium, 33% (14) thiazide diuretics, 26% (11) potassium, 7% (3) phosphate binder, 7% (3) PTH, and

5% (2) no treatment. Mean±SD fasting values collected prior to conventional therapy dose are presented. PTH concentrations (10.1±8.2 pg/mL [nl 15-65]) and albumin-corrected calcium ([cCa]=7.5±1.0 mg/dL [nl 8.5-10.5]) were low. Despite the low mean cCa, the mean 24-hr urine calcium was elevated (268±183 mg/d, [nl <250 women, <300 men]). Blood phosphate was 4.8±0.8 mg/dL [nl 2.5-4.8] while blood magnesium was 1.8±0.2 mg/dL [nl 1.8-2.4]. 25-OH vitamin D was 35.0±13.5 ng/mL [nl 30-80]. Renal function as assessed by CKD-EPIcr_R showed eGFR of 86 ±23 mL/min/1.73m² (range 36-123). This study represents the largest cohort of adults with ADH1 described to date. These data highlight variability in therapeutic approaches in a real-world setting with some participants receiving up to 6 different medications/supplements. Despite being followed in expert centers, and treated with available therapies, patients on average have low cCa with relatively high 24-hr urine calcium excretion. The CLARIFY study provides an opportunity to better understand the progression and burden of disease in participants with ADH1.

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