RESEARCH ARTICLE

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Autosomal Dominant Hypocalcemia Type 1: A Systematic Review

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ABSTRACT

Autosomal dominant hypocalcemia type 1 (ADH1) is a rare form of hypoparathyroidism due to activating variants of the calcium-sensing receptor gene (*CASR*). Inherited or *de novo* activating variants of the *CASR* alter the set point for extracellular calcium, resulting in inadequate parathyroid hormone (PTH) secretion and inappropriate renal calcium excretion leading to hypocalcemia and hypercalciuria. Conventional therapy includes calcium and activated vitamin D, which can worsen hypercalciuria, resulting in renal complications. A systematic literature review, using published reports from 1994 to 2021, was conducted to catalog *CASR* variants, to define the ADH1 clinical spectrum, and to determine the effect of treatment on patients with ADH1. There were 113 unique *CASR* variants reported, with a general lack of genotype/phenotype correlation. Clinical data were available in 191 patients; 27% lacked symptoms, 32% had mild/moderate symptoms, and 41% had severe symptoms. Seizures, the most frequent clinical presentation, occurred in 39% of patients. In patients with blood and urine chemistries available at the time of diagnosis ($n = 91$), hypocalcemia (99%), hyperphosphatemia (59%), low PTH levels (57%), and hypercalciuria (34%) were observed. Blood calcium levels were significantly lower in patients with severe symptoms compared with asymptomatic patients (6.8 ± 0.7 versus 7.6 ± 0.7 mg/dL [mean ± SD]; $p < 0.0001$), and the age of presentation was significantly lower in severely symptomatic patients (9.1 ± 15.0 versus 19.3 ± 19.4 years; $p < 0.01$). Assessments for complications including nephrocalcinosis, nephrolithiasis, renal impairment, and brain calcifications in 57 patients on conventional therapy showed that 75% had at least one complication. Hypercalciuria was associated with nephrocalcinosis, nephrolithiasis, renal impairment, or brain calcifications (odds ratio [OR] = 9.3; 95% confidence interval [CI] 2.4–37.2; $p < 0.01$). In 27 patients with urine calcium measures before and after starting conventional therapy, the incidence of hypercalciuria increased by 91% ($p < 0.05$) after therapy initiation. ADH1 is a condition often associated with severe symptomatology at presentation with an increase in the risk of renal complications after initiation of conventional therapy. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ADH1; HYPOPARATHYROIDISM; CALCIUM-SENSING RECEPTOR; HYPOCALCEMIA; CALCILYTIC

Introduction

Hypoparathyroidism is an endocrine disorder characterized by hypocalcemia, hyperphosphatemia, and inappropriately low levels of circulating parathyroid hormone (PTH). The most common cause of hypoparathyroidism is the destruction of parathyroid tissue during thyroidectomy or other neck surgeries; additional etiologies may be genetic or autoimmune. Autosomal dominant hypocalcemia type I (ADH1) (OMIM 601198) is a rare form of hypoparathyroidism resulting from inherited or *de novo* gain-of-function variants in the calcium-sensing receptor gene (*CASR*). Distinct from postsurgical hypoparathyroidism, ADH1 is often associated with more pronounced hypercalciuria, especially after the initiation of treatment. The biochemical abnormalities are explained by the role of the calcium-sensing receptor (CaSR) in regulating systemic calcium homeostasis.

Hypocalcemia resulting from hypoparathyroidism inherited in an autosomal dominant fashion has been recognized for many years.[1] Activating variants of the *CASR* were first reported as the molecular basis for ADH1 in 1994.[2] Subsequently, many kindreds with hypoparathyroidism as well as patients with sporadic hypoparathyroidism were shown to possess unique activating variants of the *CASR*.[3-5] ADH1 has an estimated prevalence ranging from 1 per 70,000[6] to 3.9 per 100,000.[7] The converse

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of ADH1, familial hypocalciuric hypercalcemia type 1 (FHH1; OMIM 145980) is characterized by inactivating variants of the *CASR*, leading to elevated blood calcium levels and low urinary calcium levels.[2] FHH1 is a condition in which patients are generally asymptomatic. Homozygous inactivating variants of the *CASR* cause neonatal severe hyperparathyroidism (NSHPT; OMIM 239200), a disease characterized by parathyroid gland hyperplasia and severe hypercalcemia and that can be fatal if a parathyroidectomy is not performed.[8]

Regulation of systemic mineral homeostasis

The CaSR is a class C, G protein-coupled receptor whose primary physiological ligand is extracellular ionized calcium (Ca^{2+}) and whose function is to detect and respond to changes in the concentration of ambient extracellular Ca^{2+}.[9] The receptor is expressed in several different tissues but is most highly expressed in the parathyroid glands and kidneys.[10] In the parathyroid glands, the CaSR is the primary regulator of PTH synthesis, secretion, and parathyroid cell proliferation.[11] Activation of the CaSR by extracellular Ca^{2+} suppresses these cellular responses. PTH secretion is thereby increased when extracellular Ca^{2+} levels fall below the normal range. PTH acts in the proximal tubule of the kidney to increase the synthesis of 1,25-dihydroxy-vitamin D_3, which acts in the small intestine to increase calcium and phosphate absorption. PTH also acts on the thick ascending limb and distal convoluted tubule of the kidney to increase the reabsorption of Ca^{2+} from the filtrate to the blood. Additionally, PTH inhibits phosphate reabsorption in the proximal tubule. Finally, PTH acts in the bone to release Ca^{2+} into the blood by promoting bone resorption. These concerted actions of PTH lead to an increase in blood Ca^{2+}, a decrease in blood phosphate, and increased levels of 1,25-dihydroxy-vitamin D_3. The increased Ca^{2+}, in turn, through a CaSR-mediated feedback loop, inhibits the secretion of PTH (Fig. 1). This inverse relationship is the essential endocrine feedback mechanism maintaining blood Ca^{2+} within a very narrow physiologic range.

In the kidney, the CaSR is expressed along the entire length of the nephron with its primary effect on regulating Ca^{2+} and magnesium (Mg^{2+}) reabsorption in the thick ascending limb and the distal convoluted tubule.[12] Activation of the CaSR decreases Ca^{2+} reabsorption by several different mechanisms. Initially, it was shown that CaSR activation blocks ion channels involved in maintaining the electrical potential to drive the paracellular movement of Ca^{2+} from the lumen to the basolateral side of the tubule.[13] More recently, certain claudins in the tight junctions between tubule cells have been shown to regulate the permeability of Ca^{2+} through the paracellular pathway.[14] Thus, there are multiple mechanisms leading to calcium loss in the urine and resultant hypercalciuria. There is also evidence that the CaSR in the proximal tubule may regulate phosphate reabsorption and 1,25-dihydroxy-vitamin D_3 synthesis either directly and/or by opposing the effects of PTH.[15]

ADH1 is a set-point disorder

The concentration of extracellular Ca^{2+} that half-maximally activates the CaSR (the EC_{50}) is approximately 1.25 mM, the level that represents normocalcemia in adults. The EC_{50} of the CaSR for extracellular Ca^{2+} is often referred to as the "set point" for systemic Ca^{2+} homeostasis, and the CaSR is sometimes referred to as the "calciostat," as it monitors and responds to

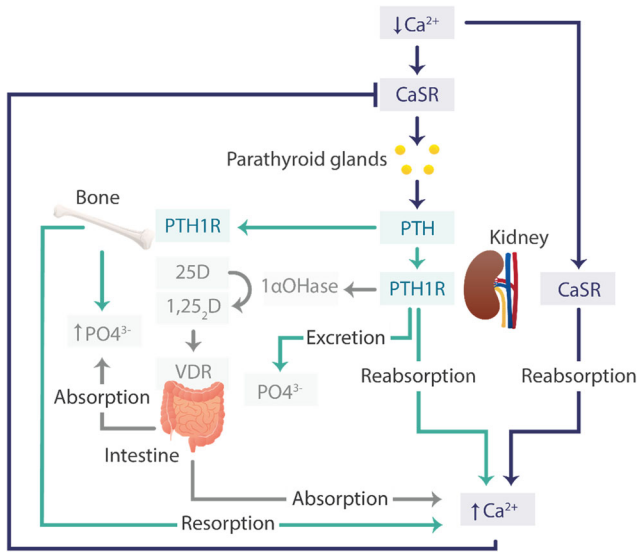

Fig. 1. Regulation of systemic mineral metabolism. CaSRs in the parathyroid glands and the kidneys play key roles regulating PTH secretion and Ca^{2+} reabsorption, respectively.

changes in extracellular Ca^{2+} concentration. Excursions in blood Ca^{2+} levels alter the activity of the CaSR, thereby changing PTH secretion and renal Ca^{2+} reabsorption to maintain blood Ca^{2+} near the set point.[14] In receptors with activating variants, the EC_{50} is lower and sensitivity to Ca^{2+} is elevated, such that lower blood Ca^{2+} levels are "sensed" as normal. Thus, PTH synthesis and secretion and renal Ca^{2+} reabsorption are decreased, leading to the biochemical state that characterizes ADH1: hypocalcemia, low or inappropriately normal PTH, and relative hypercalciuria.[16]

Symptom presentation and diagnosis

Presenting clinical signs and symptoms of ADH1 are typically those resulting from hypocalcemia, including paresthesias, muscle cramps and spasms, and tetany. More severe symptoms of arrhythmias, laryngospasm, and seizures can be life threatening. Some patients may be asymptomatic despite chronic hypocalcemia.[17] Hypoparathyroidism can also be associated with cataracts and neuropsychological symptoms, including brain fog, depression, and anxiety.[18]

The typical biochemical profile includes low blood calcium with a PTH value that is either frankly low or inappropriate for the degree of hypocalcemia, as well as relative hypercalciuria. Circulating levels of phosphate are in the high-normal range or frankly elevated, while those of 1,25-dihydroxy-vitamin D_3 are inadequate or low and those of Mg^{2+} are normal or low. Imaging studies can reveal nephrocalcinosis and/or nephrolithiasis, often associated with hypercalciuria.[16] Basal ganglia calcifications are sometimes noted on head computed tomography. Additionally, hypocalcemia and hypomagnesemia can slow cardiac ventricular repolarization, as reflected in a prolonged QT interval on the surface electrocardiogram in patients with ADH1.[19]

Medical intervention and treatment-emergent complications

Conventional treatments in symptomatic patients, which include calcium and/or activated vitamin D (which is the 1-alpha hydroxylated form of 25-OH vitamin D_3, typically calcitriol or alfacalcidol) as oral supplements, are aimed at alleviating symptoms. Although conventional therapy can increase blood levels of Ca^{2+}, supplementation in the absence of normal parathyroid function can result in or exacerbate pre-existing hypercalciuria, increasing the risk of long-term renal complications such as nephrocalcinosis, nephrolithiasis, and impaired renal function. Therefore, the goal of the conventional standard of care is to elevate blood Ca^{2+} to the low-normal or just below normal range to prevent symptoms while minimizing hypercalciuria and its long-term sequelae.

Several reviews focused on disorders resulting from variants in the *CASR* have included sections on ADH1,[20,21] and the most recent report has quantified symptoms and degree of hypocalcemia.[22] The present study expands on these efforts by including greater detail on the pathophysiology, burden of illness, and effects of treatment in patients with ADH1. As investigational new treatments for hypoparathyroidism, and ADH1 specifically, are now in clinical trials, it is important to systematically interrogate the existing literature to gain a better understanding of the phenotypic spectrum of ADH1 and the limitations associated with conventional treatment.

Materials and Methods

Literature search and data extraction

PubMed was searched for published reports of patients with ADH1 or families with confirmed activating *CASR* variants diagnosed from 1994 to 2021 using the following terms: autosomal dominant hypocalcemia, ADH1, genetic/congenital hypoparathyroidism, familial hypoparathyroidism, hypercalciuric hypocalcemia, and activating *CASR* variants. The literature search yielded 86 articles describing 339 patients with ADH1 caused by activating *CASR* variants. Clinical data were extracted from published reports of patients or families with confirmed activating *CASR* variants and ADH1 diagnoses. If available, the data collected from each study included age at clinical presentation, mode of diagnosis, nucleotide change in the *CASR* variant, presenting symptoms, pretreatment biochemical profile, on-treatment blood calcium, urine calcium, and complications. Of the total 338 patients with ADH1, 147 were excluded from the cohort analysis because of insufficient clinical information. Of the 86 articles describing patients with ADH1, 24 were excluded from the cohort analysis because of insufficient clinical information in all the ADH1 cases reported.

Cohort identification and term definitions

Individual cases were divided into three cohorts based on available clinical information (Fig. 2). Cohort 1 ($n = 191$) comprises patients with symptom onset information (age and symptoms). Cohort 2 ($n = 91$) is a subgroup of Cohort 1 with available pretreatment blood and urine Ca^{2+}, blood phosphorus, and blood PTH. Cohort 3 ($n = 57$) consists of patients with data on age, symptoms, pretreatment blood Ca^{2+}, and on-treatment outcomes including blood Ca^{2+}, urine Ca^{2+}, and complications. The presentation, which prompted a diagnosis of ADH1, was categorized as either symptomatic, part of a family screening, or incidental. Clinical presentation was divided into three categories: asymptomatic (absence of hypocalcemia-related symptoms); mild/moderate, including some combination of muscle cramps/spasms, bone/joint pain, tetany, paresthesia, brain fog, and/or fatigue; or severe, including seizures, loss of consciousness, and/or laryngospasm. Urine Ca^{2+} assessments consisted of either 24-hour urine Ca^{2+} measurements or spot urine measurements in relation to creatinine (urinary Ca^{2+}/creatinine ratio). The normal ranges for all biochemical measures were recorded as reported in the original article. If the original article did not report a normal range, standard normal ranges for the appropriate age group were used. In those few cases, 8.4 mg/dL was considered the lower limit of normal for blood Ca^{2+}, and 0.22 mg/mg was considered the upper limit of normal for urinary Ca^{2+}/creatinine ratio.[23] Associated complications consisted of nephrocalcinosis, nephrolithiasis, renal impairment, and/or basal ganglia calcifications. Renal impairment and basal ganglia calcifications were recorded as reported by the original article.

Statistical analysis

All statistical analyses were conducted using GraphPad (La Jolla, CA, USA) Prism software. For two groups, an unpaired Student's *t* test was used to determine statistical significance. For three or more groups, a one-way analysis of variance (ANOVA) with multiple comparisons was used to determine statistical significance. For the odds ratio analysis, a binary comparisons table was used.

Results

ADH1 population characteristics

The literature search yielded 86 reports describing 338 patients with ADH1 caused by activating *CASR* variants. The number of patients in each study ranged from 1 to 25. Of the total 338 patients with ADH1, 147 were excluded from analysis because of insufficient information. Among the 191 patients in Cohort 1, the median age at the time of diagnosis for a hypocalcemia-related disorder was 4 years, (range, 0–66 years; 14 ± 18 years [mean $\pm$ 1 SD]) (Table 1). Most patients (81%) were diagnosed with a hypocalcemia-related disorder before 18 years of age. The median age of complete diagnosis of hypoparathyroidism caused specifically by a *CASR* variant and thus genetically confirmed as ADH1 was 25 years (range, 0–77 years, 27 ± 20 years).

Etiology

Although the majority of identified cases were familial (78%), *de novo* activating variants of *CASR* were also identified (20%), followed by germline mosaicism (1%), or unknown inheritance (1%). Only one report described a patient with ADH1 with a homozygous *CASR* variant[24]; all other ADH1 variants had a heterozygous pattern.

Diagnosis and symptom presentation

Patients with ADH1 were frequently given an initial incomplete diagnosis of idiopathic hypoparathyroidism or hypocalcemia (93%). A small number were misdiagnosed with a seizure, respiratory-related, or cardiovascular-related disorder (7%). Symptom presentation (71%), family screening (23%), or incidentally discovered hypocalcemia (6%) resulted in an initial

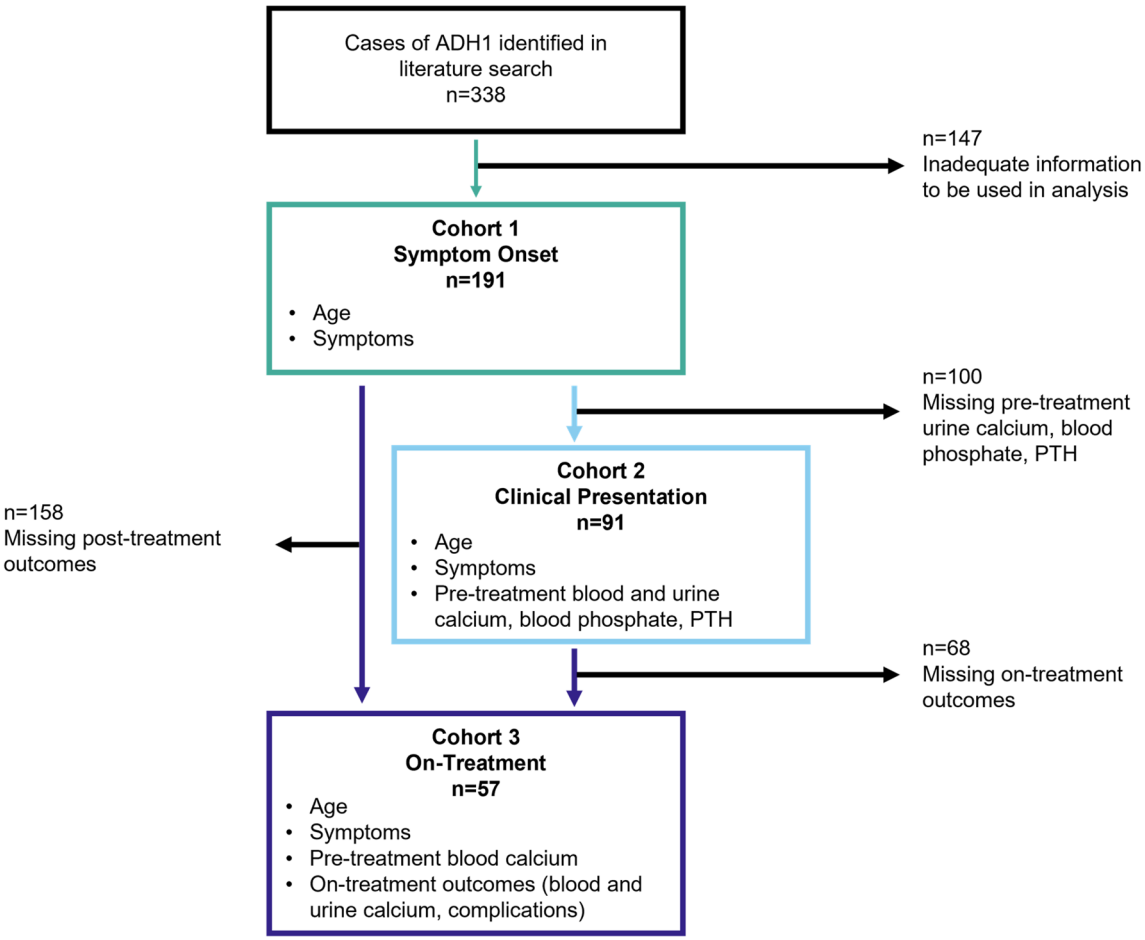

Fig. 2. Flow chart for ADH1 case inclusion and exclusion criteria. ADH1 cases ($n = 338$) were identified from a literature search. ADH1 cases with inadequate information ($n = 147$) were excluded from the analysis.

Table 1. Characteristics of Individuals With ADH1 (Cohort 1)

	Reported cases (cohort 1)
Age (years) at diagnosis of a hypocalcemia-related disorder, median (range)	4 (0–66)
Age (years) at diagnosis of ADH1, median (range)	25 (0–77)
Primary driver of diagnosis (%)	
Symptoms	71%
Family screen	23%
Incidental	6%
Symptom burden (%)	
Asymptomatic	27%
Moderate	32%
Severe	41%

Primary driver of diagnosis refers to the main factor contributing to a diagnosis of a hypocalcemia-related disorder. Asymptomatic symptom burden refers to the absence of hypocalcemia-related symptoms. Moderate symptom burden includes muscle cramps/spasms, bone/joint pain, tetany, paresthesia, brain fog, and/or fatigue. Severe symptom burden includes seizures, loss of consciousness, and/or laryngospasm.

diagnosis of a hypocalcemia-related disorder. The clinical presentation of ADH1 was primarily attributed to hypocalcemia and graded as asymptomatic (27%), moderate (32%), or severe (41%) (Table 1). The most frequent clinical presentation was a seizure, which occurred in 39% of patients. The mean age of presentation was lower in severe ADH1 cases compared with moderate and asymptomatic cases (9.1 ± 15.0 versus 19.3 ± 19.4 years; $p < 0.01$).

Biochemical markers

Among the 91 patients in Cohort 2 with reported biochemistries, severe ADH1 cases exhibited significantly lower mean blood calcium levels (6.8 ± 0.7 mg/dL) compared with both asymptomatic (7.6 ± 0.7 mg/dL; $p < .0001$) and moderately symptomatic patients with ADH1 (7.4 ± 0.5 mg/dL; $p < 0.01$) (Fig. 3). The mean blood calcium levels associated with moderate and asymptomatic ADH1 cases were not significantly different ($p = 0.1$) (Fig. 3). In addition to hypocalcemia, other biochemical features were associated with symptoms. Hyperphosphatemia was associated with moderate and severe clinical manifestations of ADH1 (odds ratio [OR] = 2.7, 95% confidence interval [CI] 1.2–6.3, $p < 0.05$) and severe ADH1 manifestations alone (OR = 4.3, 95% CI 1.3–12.9, $p < 0.05$). Hypercalciuria was associated with moderate and severe clinical ADH1 manifestations (OR = 4.5, 95% CI 1.8–10.8, $p < 0.01$). At the time of presentation,

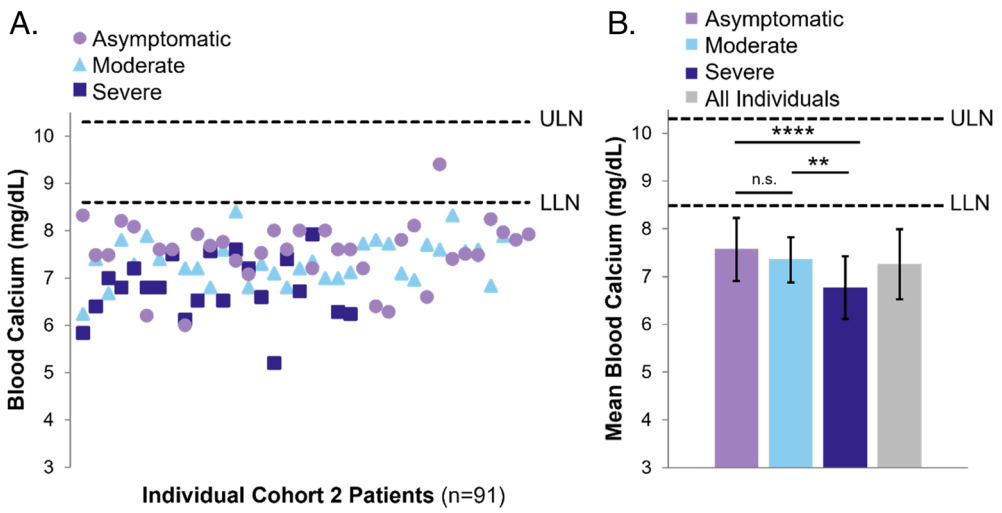

Fig. 3. Blood calcium levels at the time of presentation. (*A*) Blood calcium levels for all patients in cohort 2. (*B*) Average blood calcium for asymptomatic, moderate, severe, and all patients in cohort 2. Data presented as mean ± SD. Statistical significance was determined using a one-way ANOVA with multiple comparisons. ULN = upper limit of normal; LLN = lower limit of normal; n.s. = not significant ($p = 0.1147$); $^{**}p < 0.01$; and $^{****}p < 0.0001$.

hypocalcemia was observed in 99% of patients with ADH1 (Fig. 4). Hyperphosphatemia (59%), low PTH, defined as below the lower limit of normal based on the reference range provided in the original article (57%), and hypercalciuria (34%) were also observed (Fig. 4).

Genotype–phenotype relationship

There were 113 different *CASR* gain-of-function variants described in the 338 cases of ADH1. Variants were present throughout the expressed protein sequence, but most (55%) were in the extracellular domain (ECD), 33% were within the transmembrane domains, and 12% were in the intracellular tail. By far the most common variants in *CASR* were single-nucleotide substitutions resulting in missense variants (95%). There were six deletion variants and one nonsense variant. The most common missense variant in the protein was P221L in the ECD, which was present in 8% of the kindreds with ADH1 (Supplemental Table S1 and Supplemental Fig. S1).

Some variants are associated with a very severe phenotype, with biochemistries resembling those found in certain Bartter's syndromes. In fact, until recently, these *CASR* variants were considered to be the genetic basis for Bartter's syndrome type V.[25] All five of the Bartter's syndromes result from variants in the genes for ion channels or proteins that affect the function of ion channels in the renal cortical thick ascending limb or distal

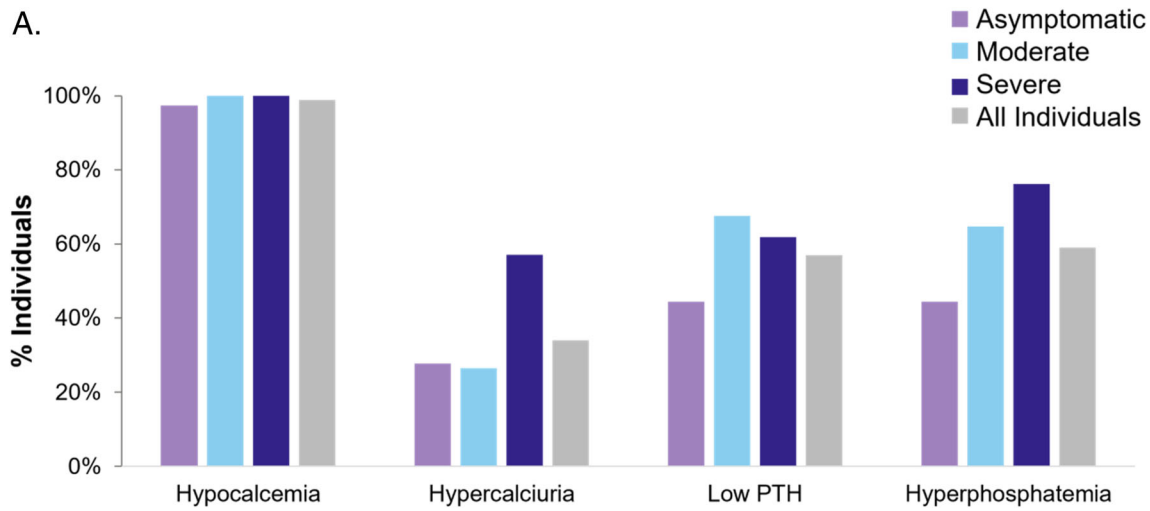

Fig. 4. Biochemical features at the time of presentation. Observation of hypocalcemia, hypercalciuria, low PTH, and hyperphosphatemia for asymptomatic, moderate, severe, and all patients in cohort 2. Sample size: $n = 36$ asymptomatic; $n = 34$ moderate symptomatic; $n = 21$ severe symptomatic (total $n = 91$).

convoluted tubule.[26] These channels contribute to electrolyte balance and, when impaired, lead to salt-wasting and hypokalemia with secondary hyperreninemia, hyperaldosteronism, and metabolic alkalosis. The *CASR* variant that seems to be invariably associated with a severe clinical phenotype is A843E. At least seven cases harboring this variant have been reported, and all were symptomatic and had varying degrees of electrolyte abnormalities.[5,26-30] The A843E variant is constitutively active when expressed in HEK-293 cells and transcription of this variant *CASR* therefore results in a receptor that always retains some activity regardless of the concentration of extracellular Ca^{2+}.[31] Several other variants identified in Supplemental Table S1 have been associated with Bartter's-like syndromes, although the degree of electrolyte disturbances and metabolic alkalosis vary even among patients with the same genotype.

Aside from these severe Bartter's cases, there was no obvious correlation between most genotypes and clinical phenotypes. For example, in the 25 patients with the P221L variant, 13 were asymptomatic and 9 were symptomatic (clinical symptoms were not reported in 3 other cases). Of those who were symptomatic, 5 had mild/moderate symptoms and 4 had severe symptoms. Even siblings with ADH1 can have markedly different clinical presentations despite harboring the same genotype.[5,32] One reported case of ADH1 with a homozygous genotype presented with moderate hypocalcemia and mild symptoms.[24]

Medical intervention and treatment-emergent complications

Among the 57 patients in Cohort 3 with assessments of on-treatment complications, 59% were prescribed activated vitamin D supplementation, 2% were prescribed calcium supplementation, and 39% were prescribed both activated vitamin D and calcium supplementation (Fig. 5*A*). Thiazides were prescribed to 21% of ADH1 cases, in conjunction with calcium and activated vitamin D supplementation, to reduce urine calcium excretion. Magnesium supplements were prescribed to 14% of ADH1 cases. The mean on-treatment blood Ca^{2+} levels in Cohort 3 increased 25% compared with pretreatment (8.1 $\pm$ 1.0 mg/dL versus 6.5 $\pm$ 1.1 mg/dL, respectively); on-treatment mean blood Ca^{2+} concentrations were in the normal range in 23% of patients. Hypercalciuria was observed in 62% of patients and at least one complication was found in 75% of patients while on-treatment. Hypercalciuria was associated with renal complications including nephrocalcinosis, nephrolithiasis, and renal impairment, as well as basal ganglia calcifications (OR = 9.3; 95% CI 2.4–37.2; $p < 0.01$; Fig. 5*B*). On-treatment blood Ca^{2+} levels were not found to be associated with complications. Nephrocalcinosis and/or nephrolithiasis were the most common complications occurring in 70% of treated patients assessed for nephrocalcinosis and/or nephrolithiasis ($n = 51$). Renal impairment was observed in 57% of treated patients assessed for renal impairment ($n = 23$, Fig. 5*C*). Basal ganglia calcifications were observed in 38% of treated patients assessed for basal ganglia calcifications ($n = 21$, Fig. 5*C*). In a subset of 27 patients from Cohort 3 with pretreatment and on-treatment urine Ca^{2+} measures, the incidence of hypercalciuria increased by 91% ($p < 0.05$, Fig. 5*D*). At least one episode of hypercalcemia occurred in 57% of the 14 treated patients who were assessed for hypercalcemic episodes.[5] Cataracts were not observed in treated patients assessed for cataracts ($n = 2$). Hypertension was not observed in any treated patients assessed for hypertension ($n = 3$). Prolonged QT interval was observed in 100% of treated patients with QT interval assessed ($n = 2$).

Winer and colleagues investigated both once-daily and twice-daily subcutaneous PTH 1-34 (teriparatide) in adults and children with hypoparathyroidism due to several different etiologies including ADH1.[33] In this study, twice-daily injection of teriparatide significantly improved blood Ca^{2+} levels in patients with ADH1 compared with once-daily teriparatide treatment (7.8 $\pm$ 0.62 mg/dL versus 6.8 $\pm$ 0.50 mg/dL, respectively). Significantly higher doses of PTH were required to raise blood Ca^{2+} levels into, or close to, the normal range in patients with ADH1 compared with those with other causes of hypoparathyroidism. However, patients with ADH1 exhibited significantly higher urine Ca^{2+} levels with twice-daily teriparatide treatment compared with once-daily teriparatide treatment after administration of the second dose.[33] Winer and colleagues also investigated teriparatide delivered via twice-daily injection versus continuous subcutaneous infusion in children with severe congenital hypoparathyroidism, including 7 patients with ADH1. Overall, PTH 1-34 delivered via infusion pump produced near normalization of blood Ca^{2+} versus twice-daily PTH 1-34 (8.3 $\pm$ 0.21 mg/dL versus 7.7 $\pm$ 0.12 mg/dL, respectively). However, in the subset of children with ADH1, there was no difference in urine Ca^{2+} excretion to blood Ca^{2+} ratio between the two dosing regimens, suggesting that PTH replacement is unable to correct hypercalciuria in patients with *CASR* mutations.[34]

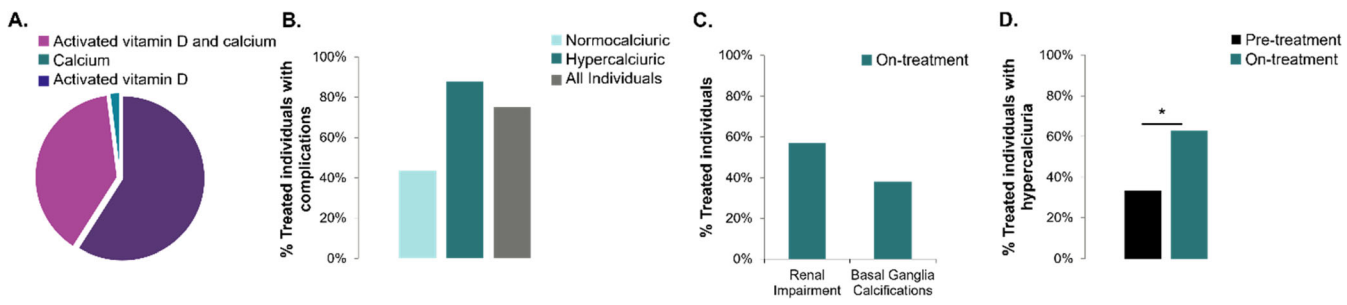

Fig. 5. ADH1 conventional therapy. (*A*) Treatment regimens for patients in cohort 3 ($n = 57$). (*B*) Complications observed on-treatment in normocalciuric, hypercalciuric, and all treated patients. Complications assessed include nephrocalcinosis, nephrolithiasis, renal impairment, and/or basal ganglia calcifications. (*C*) Rate of renal impairment ($n = 23$) and basal ganglia calcifications ($n = 21$) in a subset of patients in cohort 3. (*D*) Incidence of hypercalciuria pretreatment and on-treatment for a subset of patients in cohort 3 ($n = 27$). Statistical significance was determined using a McNemar's test. *$p = 0.0433$.

Recently, Sastre and colleagues[35] reported the effectiveness of continuous subcutaneous PTH 1-34 infusion in a cohort of 6 patients with ADH1 and hypocalcemic seizures who had previously received calcium and activated vitamin D, intermittent PTH injections, or both. In this study, continuous subcutaneous PTH 1-34 infusion resulted in an increase in blood Ca^{2+} by 1.2 mg/dL (95% CI 0.12–0.48) compared with blood Ca^{2+} levels in the same patients during treatment with standard of care (calcium and activated vitamin D). PTH infusion substantially reduced the number of seizures from 2.0 per month (95% CI −1.6 to 5.6) to 0.01 per month (95% CI −0.01 to 0.02), resulting in fewer emergency hospital admissions. One-half of the patients studied harbored variants that resulted in receptors that were constitutively active (2 patients with the A843E and 1 with the Y829C variant), demonstrating the effectiveness of this treatment even in severe cases of ADH1. Treatment with PTH infusion did not worsen nephrocalcinosis or increase urine Ca^{2+} excretion. Urine Ca^{2+} excretion was nominally reduced, but urine Ca^{2+} levels did not appear to normalize with continuous PTH infusion.[36]

Teriparatide has not been approved for the treatment of hypoparathyroidism or ADH1. Full-length PTH 1-84 (Natpara) has been approved as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism, but patients with ADH1 were specifically excluded in studies with PTH 1-84.[37]

Emerging therapies for hypoparathyroidism

There are a number of potential new therapies for hypoparathyroidism currently in development that may be useful in treating patients with ADH1. The peptide furthest along is a form of PTH 1-34 that has been conjugated to methoxy polyethylene glycol (palopegteriparatide [TransCon PTH]).[38] Recently presented data from the 6-month time point of the ongoing open-label extension of the phase 2 trial suggested that palopegteriparatide was well tolerated and maintained blood Ca^{2+} in the normal range, reduced 24-hour urine Ca^{2+}, eliminated the need for activated vitamin D, and decreased the need for supplemental calcium.[38-40] No data regarding palopegteriparatide treatment in patients with ADH1 have been reported.

A phase 1 clinical trial in healthy men showed that a single injection of AZP-3601, a 36-amino acid long-acting PTH analogue, increased blood Ca^{2+} levels for up to 24 hours.[41] The peptide LY627-2 K is another teriparatide analogue conjugated to polyethylene glycol,[42] which has shown promising results in animal studies. An orally active formulation of teriparatide studied in patients with hypoparathyroidism reduced the number of daily calcium supplements required but did not increase blood Ca^{2+} levels.[43] Additionally, an orally active, small-molecule agonist of the PTHR1, PCO371, has been shown to increase blood Ca^{2+} and decrease blood phosphate in parathyroidectomized rats,[44] but the clinical trial was terminated because of an uncertain risk–benefit balance for the patients.[45]

A novel approach is the use of calcilytics to treat hypoparathyroidism. Calcilytics are CaSR antagonists, and most are negative allosteric modulators of the CaSR that decrease the sensitivity of CaSR to activation by extracellular Ca^{2+}, thereby increasing the secretion of PTH. As calcilytics shift the EC_{50} for extracellular Ca^{2+} to higher levels, they have the potential to address the underlying genetic defect that causes ADH1. Calcilytics have been studied as potential treatments for ADH1.[46,47] A proof-of-concept trial in patients with ADH1 using an intravenously infused calcilytic (NPSP795) demonstrated a dose-dependent increase in blood PTH levels in patients with ADH1.[46]

A -Pase 2b open-label extension trial with the calcilytic encaleret (CLTX-305) is currently underway to evaluate the safety and efficacy of this orally administered investigational calcilytic in ADH1.[48] Preliminary results indicate that encaleret increases blood PTH levels leading to normalization of albumin-corrected blood Ca^{2+} and decreases blood phosphate on day 5 of treatment. Urine Ca^{2+} levels were elevated at study entry and decreased into the sex-specific normal range by day 5 of treatment. All supplemental calcium and activated vitamin D were discontinued before initiation of encaleret.[47]

Discussion

We have summarized the literature on patients with ADH1 to date with a focus on clinical presentation, treatment outcomes, and complications. The 338 cases reviewed, which to our knowledge encompass all the published cases of ADH1, are composed of 113 distinct *CASR* variants.

Presenting symptoms were heterogeneous across the population of patients with ADH1. Although just under one-third of the patients were asymptomatic, more than one-third presented with at least one severe symptom, which included seizure, loss of consciousness, and/or laryngospasm. It is noteworthy that the most common presentation was a seizure, which can be life threatening. The severity of these presenting symptoms argues for the importance of early recognition and diagnosis of ADH1. As would be expected, the age of diagnosis and the presenting Ca^{2+} level was lower in severely symptomatic patients, yielding a smaller window to diagnose ADH1 before a potentially life-threatening event. Although the median age of diagnosis of a hypocalcemia-related disorder was 5 years, the median age at the time of a complete diagnosis of ADH1 was not until age 24, illuminating the delay in the specific diagnosis of ADH1. Almost all patients were initially given an incomplete diagnosis of idiopathic hypoparathyroidism or hypocalcemia.

On presentation, almost all patients had hypocalcemia, but it is noteworthy that more than one-third had frank hypercalciuria, and two-thirds had inappropriately normal urinary Ca^{2+}, despite being hypocalcemic and not on treatment. In the absence of gain-of-function *CASR* variants, patients with hypocalcemia typically have low urine Ca^{2+} levels.[16] These baseline elevations in urine calcium in patients with ADH1 separate ADH1 from other hypocalcemic disorders and highlight the need for urine Ca^{2+} monitoring.[16] These urine assessments are limited by collection method, as some studies used spot urine Ca^{2+}: creatinine ratios, which are generally not well correlated with 24-hour urine collections, the gold standard for the diagnosis of hypercalciuria. Although just more than half of patients were reported to have PTH levels below the lower limit of normal, any "normal" PTH level is inappropriately low when occurring simultaneously with hypocalcemia.

Conventional treatment with either calcium, activated vitamin D, or a combination of the two raised blood Ca^{2+} and alleviated symptoms of hypocalcemia in about two-thirds of patients, but the resultant increased filtered load of calcium worsened hypercalciuria and increased renal complications. The underlying cause of symptoms and complications in patients with activating *CASR* variants is twofold. The first is absolute hypocalcemia that results in symptoms like tetany and seizures. The second is a physiologically perceived hypercalcemia

due to the altered CaSR set point that results in renal complications. For this reason, the goal of treatment with conventional therapy should be focused on alleviating the signs and symptoms of hypocalcemia rather than restoring normocalcemia.

With this in mind, we collected data on complications including nephrocalcinosis, nephrolithiasis, renal impairment, and basal ganglia calcifications, as reported by the original article; three-quarters of treated patients were found to have at least one complication. Not surprisingly, the presence of hypercalciuria was significantly associated with complications. The presence of nephrolithiasis and/or nephrocalcinosis in more than half of patients and even renal impairment in treated patients stresses the importance of renal monitoring in patients with ADH1, especially those on treatment. Again, proper diagnosis of ADH1 is crucial to setting realistic treatment goals to monitor and minimize renal complications.

No currently approved therapy can correct absolute hypocalcemia in the setting of a perceived normo- or hypercalcemia. Existing therapies like calcitriol, by correcting the absolute hypocalcemia, often aggravate the condition by augmenting the perceived state of hypercalcemia.

Surprisingly, although the vast majority of cases were familial with an autosomal dominant inheritance pattern, only about a quarter of cases were detected because of family screening, and 71% of cases were identified only after the patient presented with clinical symptoms. It is possible that both symptom-driven diagnoses and the lag time between a hypocalcemia-related diagnosis and ADH1 are due to a historical difficulty in obtaining genetic testing. With greater availability of genetic testing, accurate diagnosis of diseases such as ADH1 might be accelerated in the future. Patients with "idiopathic hypoparathyroidism" should undergo genetic testing as identification of a genetic condition, such as ADH1, has direct implications on the clinical and/or genetic evaluation of related relatives, might avoid severe presenting symptoms such as seizure, and aid in family planning, including preimplantation testing. Genetic testing should be performed in conjunction with genetic counseling to help interpret results. The importance of a specific diagnosis of ADH1 is amplified because of the associated hypercalciuria. Monitoring of urine Ca^{2+}calcium is of increased significance in these patients, especially in the context of treatment, which should be carefully monitored to decrease the risk of renal complications.

There was a general lack of genotype/phenotype correlation, and in some cases, family members with the same variant had quite different clinical presentations. Patients with variants in the *CASR* that cause large decreases in the EC_{50} in vitro and thus large increases in the sensitivity to extracellular Ca^{2+} can present with a low-normal blood Ca^{2+} level and be asymptomatic. Conversely, variants that cause very small increases in the sensitivity to extracellular Ca^{2+} can be associated with profound laboratory values, including frank hypercalciuria and severe symptoms of hypocalcemia.[17] This is an important observation indicating that genotype alone should not be used to make treatment or surveillance decisions. Patients should have medication regimens individualized to their clinical features.

Seven of the variants, however, especially the constitutively active A843E, are associated with a very severe phenotype akin to a Bartter's syndrome. It is known that some *CASR* variants can preferentially couple to particular signaling pathways.[22,49] Perhaps these "hyperactive" receptors that result in a very severe phenotype lead to inhibition of the Na-K-Cl cotransporter and renal outer medullary potassium channel to alter electrolyte balance, whereas less severe *CASR* variants affect predominantly the claudin mechanisms. Because the claudin mechanisms preferentially affect Ca^{2+} reabsorption, patients with less severe *CASR* variants have hypercalciuria unaccompanied by additional electrolyte disturbances.

Only one reported case of homozygosity for *CASR* gain-of-function variants was reported, and there are insufficient data to determine the effects of homozygous gain-of-function variants. This lack of reported cases could be explained by the rare prevalence of ADH1 or perhaps homozygosity could lead to neonatal lethality.

This study is an exhaustive systematic assessment of patients with ADH1, but it has several limitations. Characteristic of other complications of observational data, these data were compiled from multiple sources and not all collected in a similar manner. The endpoints were not consistent, and different variables were described across studies. For example, while we pooled patients and analyzed patient complications after treatment, the duration of treatment varied between patients, and the timing of measurements after treatment was not standardized. The dose regimens and treatment targets also varied and were often not clearly described. We were unable to track the titration of medication and its effects on treatment outcomes or analyze the effects of each treatment regimen on laboratory parameters. We also lacked the data necessary to analyze parameters such as post-treatment blood phosphate or calcium phosphate product. Some cases with inadequate clinical information had to be excluded from the analysis. Finally, there is a selection bias in the literature in which more severe, symptomatic cases are typically selected for publication, especially after hundreds of cases are represented in the literature. Thus, the literature is likely skewed toward more symptomatic cases. In the initial report showing that variants of the *CASR* result in ADH1, Pollak and colleagues reported that only 1 of 16 affected family members had symptoms of hypocalcemia,[2] but in Pearce and colleagues, 11 of 20 individuals were symptomatic.[3] It is possible that a large survey of genomic data might reveal more asymptomatic individuals. Although Dershem and colleagues surveyed a large database of genomic sequencing finding 3 individuals with *CASR* variants and low serum calcium levels, symptoms were not documented.[7] Our literature review does align with that of Gorvin, which found 28% of patients to be asymptomatic,[22] but again, a selection bias in the literature would predict this similarity with more symptomatic cases being preferentially reported. Typically in our experience at the NIH, when asymptomatic patients are incidentally diagnosed, they reveal that they have been unknowingly symptomatic and feel better with treatment. In the future, we hope to study patients with ADH1 prospectively and collect standardized data on disease symptomatology and comorbidities, such as monitoring the development of renal calcifications and assessing the relationship to treatment parameters and duration.

Conclusion

In this systematic review, we performed a detailed analysis of 191 of the 338 published cases of ADH1. The findings illustrate the key features of ADH1, which include phenotypic heterogeneity, relatively higher baseline urinary Ca^{2+} that is exacerbated with conventional treatment, and subsequent complications such as nephrolithiasis, nephrocalcinosis, and renal impairment, as well as basal ganglia calcifications. Early, accurate diagnosis of

ADH1 is important as it might improve treatment and monitoring and ultimately decrease complications. The high complication rate combined with the fact that only 59% of patients reported symptom alleviation while on treatment not only argues for careful monitoring of patients with ADH1 on conventional treatment but also indicates the need for novel therapies, such as calcilytics and palopegteriparatide [TransCon PTH]. TransConPTH, because it is a long-acting form of teriparatide, avoids the large swings in circulating levels of PTH or teriparatide that occur after singe injections and thus more closely mimics the physiological regulation of systemic Ca^{2+} homeostasis. Calcilytics target the specific molecular lesion of ADH1 at both the parathyroid glands and kidneys and have the potential to correct the set-point disorder that characterizes ADH1. There are thus a number of new therapies that may offer advantages over conventional therapy in treating ADH1.

Disclosures

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Author Contributions

KL Roszko: Methodology; writing – original draft; writing – review and editing. **LM Stapleton Smith:** Data curation; methodology; writing – original draft; writing – review and editing. **AV Sridhar:** Resources; supervision; writing – review and editing. **MS Roberts:** Writing – review and editing. **IR Hartley:** Writing – review and editing. **RI Gafni:** Writing – original draft; writing – review and editing. **MT Collins:** Resources; writing – review and editing. **JC Fox:** Resources; writing – review and editing. **EF Nemeth:** Data curation; methodology; writing – original draft; writing – review & editing.

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Data sharing requirements are not applicable to this article because the data were synthesized from previously published reports.

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