Autosomal Dominant Hypocalcemia Type 1 (ADH1) Associated With Myoclonus and Intracerebral Calcifications

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Abstract
Autosomal dominant hypocalcemia type 1 (ADH1) is a disorder of extracellular calcium homeostasis caused by germline gain-of-function mutations of the calcium-sensing receptor (CaSR). More than 35% of ADH1 patients have intracerebral calcifications predominantly affecting the basal ganglia. The clinical consequences of such calcifications remain to be fully characterized, although the majority of patients with these calcifications are considered to be asymptomatic. We report a 20-year-old female proband with a severe form of ADH1 associated with recurrent hypocalcemic and hypercalcemic episodes, persistent childhood hyperphosphatemia, and a low calcium/phosphate ratio. From the age of 18 years, she had experienced recurrent myoclonic jerks affecting the upper limbs that were not associated with epileptic seizures, extrapyramidal features, cognitive impairment, or alterations in serum calcium concentrations. Computed tomography (CT) scans revealed calcifications of the globus pallidus regions of the basal ganglia bilaterally, and also the frontal lobes at the gray-white matter junction, and posterior horn choroid plexuses. The patient’s myoclonus resolved following treatment with levetiracetam. CASR mutational analysis identified a reported germline gain-of-function heterozygous missense mutation, c.2363T>G; p.(Phe788Cys), which affects an evolutionarily conserved phenylalanine residue located in transmembrane domain helix 5 of the CaSR protein. Analysis of the cryo-electron microscopy CaSR structure predicted the wild-type Phe788 residue to form interactions with neighboring phenylalanine residues, which likely maintain the CaSR in an inactive state. The p.(Phe788Cys) mutation was predicted to disrupt these interactions, thereby leading to CaSR activation. These findings reveal myoclonus as a novel finding in an ADH1 patient with intracerebral calcifications.

Key Words: calcium-sensing receptor, gain-of-function, basal ganglia, hypocalcemia, hyperphosphatemia

Abbreviations: ADH1, autosomal dominant hypocalcemia type 1; CaSR, calcium-sensing receptor; CT, computed tomography; PTH, parathyroid hormone; TM, transmembrane.

Autosomal dominant hypocalcemia type 1 (ADH1; OMIM #601198) is a disorder of extracellular calcium homeostasis caused by germline gain-of-function mutations of the calcium-sensing receptor (CaSR) [1, 2]. This class C G-protein coupled receptor is highly expressed in the parathyroid glands and renal thick ascending limb of the Loop of Henle, where it plays a pivotal role in regulating circulating calcium concentrations by altering parathyroid hormone (PTH) secretion and urinary calcium excretion, respectively [3-5]. ADH1 has an estimated prevalence of 3.9 per 100 000 [6] and is characterized by a biochemical phenotype that is similar to hypoparathyroidism, with features such as persistent hypocalcemia, increased circulating phosphate concentrations, and inappropriately normal or low PTH concentrations [7]. ADH1 patients also have hypomagnesemia and a relative hypercalciuria with urinary calcium to creatinine ratios that are within or above the reference range [1, 8-10]. ADH1 has a substantial burden of illness and may present in infancy, childhood, or adulthood with hypocalcemic symptoms such as paresthesia, carpopedal spasms, muscle cramps, or recurrent seizures, in ~50% of patient [9, 11, 12]. Some ADH1 patients have also been reported to suffer from arthralgia, fatigue, abdominal pain, and low mood [13, 14]. Moreover, patients with severe forms of ADH1 can develop a Bartter-like syndrome characterized by hypokalemic alkalosis, renal salt wasting, and hyperreninemic hyperaldosteronism [15, 16]. Ectopic calcifications are also a feature of ADH1, with intracerebral calcifications and nephrocalcinosis reported in > 35% and > 10% of patients, respectively [9]. Intracerebral calcifications, which predominantly affect the basal ganglia, have been detected in adults and children with ADH1, and are reported to occur as early as the first year of life [9, 17]. However, the clinical consequences of ectopic brain calcifications in ADH1 patients remain to be elucidated. We report a case of a patient with ADH1 who developed myoclonus in association with multiple intracerebral calcifications.

Case Presentation
The proband is a 20-year-old woman who was diagnosed at age 8 months with hypocalcemia after presenting with recurrent seizures. She was commenced on oral calcitriol and remained to be fully characterized, although the majority of patients with these calcifications are considered to be asymptomatic. We report a 20-year-old female proband with a severe form of ADH1 associated with recurrent hypocalcemic and hypercalcemic episodes, persistent childhood hyperphosphatemia, and a low calcium/phosphate ratio. From the age of 18 years, she had experienced recurrent myoclonic jerks affecting the upper limbs that were not associated with epileptic seizures, extrapyramidal features, cognitive impairment, or alterations in serum calcium concentrations. Computed tomography (CT) scans revealed calcifications of the globus pallidus regions of the basal ganglia bilaterally, and also the frontal lobes at the gray-white matter junction, and posterior horn choroid plexuses. The patient’s myoclonus resolved following treatment with levetiracetam. CASR mutational analysis identified a reported germline gain-of-function heterozygous missense mutation, c.2363T>G; p.(Phe788Cys), which affects an evolutionarily conserved phenylalanine residue located in transmembrane domain helix 5 of the CaSR protein. Analysis of the cryo-electron microscopy CaSR structure predicted the wild-type Phe788 residue to form interactions with neighboring phenylalanine residues, which likely maintain the CaSR in an inactive state. The p.(Phe788Cys) mutation was predicted to disrupt these interactions, thereby leading to CaSR activation. These findings reveal myoclonus as a novel finding in an ADH1 patient with intracerebral calcifications.

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remained low, typically between 1.60 and 1.80 mmol/L (normal range, 2.10-2.55), and were associated with low serum PTH concentrations (Table 1). No dysmorphic features or other clinical abnormalities were detected. There was no family history of hypocalcemia or other endocrinopathies. Cytogenetic analysis of chromosome 22 did not reveal any abnormalities associated with DiGeorge syndrome [7]. A diagnosis of congenital idiopathic hypoparathyroidism was made. Childhood growth and development were normal with no further seizures since age 4 years and no renal calculi. However, serum calcium concentrations were labile, ranging from 1.37 mmol/L to 3.24 mmol/L, and were associated with persistent hyperphosphatemia and also hypomagnesemia (Table 1, Fig. 1). An analysis of matched serum calcium and phosphate values measured throughout the proband’s life (n = 252 values) did not show any correlation with her oral calcitriol or calcium doses (Fig. 1). Moreover, the median calcium x phosphate product was normal at 3.3 mmol/L² (normal < 4.4 mmol/L²). In contrast, the median calcium to phosphate ratio was low at 1.1 mmol/mmol when compared with a reported range of 1.6 to 3.4 mmol/mmol for adult control subjects [18]. Furthermore, the proband was hypercalcuiic, and a 24-hour urine calcium excretion, measured when she was age 14 years, was elevated at 16.2 mmol/24 hours (normal < 6.5).

At 18 years of age, the proband began experiencing recurrent episodes of myoclonus, characterized by jerking movements, particularly affecting her upper limbs. These episodes were not associated with epileptic seizures and were unrelated to alterations of her serum calcium concentrations. Clinical assessment did not reveal any cognitive impairment or psychiatric symptoms. Blood pressure was 98/70 mmHg with a postural drop to 82/64 mmHg. Muscle strength was normal, and there were no Parkinsonian features. Serum biochemical assessment undertaken while the patient was on treatment with calcitriol 1 mcg twice daily, calcium carbonate 500 mg once daily, and magnesium carbonate and oxide 375 mg 2 tablets once daily, revealed her to have normal albumin-adjusted serum calcium of 2.23 mmol/L, low magnesium of 0.58 mmol/L (normal, 0.75-1.0), raised creatinine of 107 μmol/L (normal, 45-90) and eGFR of 60 mL/min/1.73m² (Table 1). No biochemical features of Bartter’s syndrome were present (Table 1). Urine calcium excretion was increased (Table 1), and renal ultrasound showed normal kidney size with increased echogenicity of the renal medulla bilaterally consistent with nephrocalcinosis or medullary sponge kidney. Bilateral renal cysts, up to 1.6 cm in size, were also detected on ultrasound. Neurological investigations consisting of lumbar puncture and electroencephalography (EEG) were unremarkable. However, CT brain imaging demonstrated central calcifications within the globus pallidus regions of the basal ganglia bilaterally, and also in the frontal lobes at the gray-white matter junction, and posterior horn choroid plexuses (Fig. 2). The patient was treated with levetiracetam 500 mg twice daily, which is an anti-epileptic and antitymyoclonic agent [19], and this resolved her myoclonic symptoms.

To establish the underlying diagnosis in the proband, CASR gene sequencing was performed by analysis of peripheral blood leukocyte DNA using an Ampliseq-for-Illumina next-generation sequencing custom panel on an Illumina MiSeq instrument. This identified a reported germline gain-of-function heterozygous CASR missense mutation, c.2363T>G; p.(Phe788Cys) [17, 20], which affects an evolutionarily conserved phenylalanine residue located in transmembrane (TM) helix 5 of the CaSR protein (Fig. 3) [2]. The recently reported cryo-electron microscopy

| Table 1. Plasma and urine biochemistry in the ADH1 proband |
|-------------------------------------------------------------|
| Serum/plasma:                                               |
| Albumin-adjusted calcium (mmol/L)                           |
| Phosphate (mmol/L)                                         |
| Ca × P (mmol²/L²)                                          |
| Ca/P (mmol/mmol)                                          |
| Magnesium (mmol/L)                                        |
| Creatinine (μmol/L)                                       |
| Parathyroid hormone (pmol/L)                              |
| Potassium (mmol/L)                                        |
| Bicarbonate (mmol/L)                                      |
| pH                                                          |
| Renin (ng/mL/hr)                                          |
| Aldosterone (pmol/L)                                      |
| Urine:                                                     |
| Calcium (mmol/24hr)                                       |
| CCRR                                                       |

| Earliest available values (age 11 months) | Lowest serum calcium (age 10 years) | Assessment for myoclonus (age 20 years) |
|------------------------------------------|-------------------------------------|----------------------------------------|
| 1.62                                     | 1.37                                | 2.23                                   |
| 2.38                                     | 2.80                                | 1.03                                   |
| 3.9                                      | 3.8                                 | 2.3                                    |
| 0.68                                     | 0.49                                | 2.17                                   |
| 0.43                                     | 0.43                                | 0.58                                   |
| 20                                       | 49                                  | 107                                    |
| 0.6                                      | -                                   | <0.4                                   |
| 4.2                                      | -                                   | 3.6                                    |
| -                                        | -                                   | 27.5                                   |
| -                                        | -                                   | 7.40                                   |
| -                                        | -                                   | 1.0                                    |
| -                                        | -                                   | 58.0                                   |
| -                                        | -                                   | 9.6                                    |
| -                                        | -                                   | 0.04                                   |

Normal serum/plasma ranges: albumin-adjusted calcium, 2.10-2.55 mmol/L; phosphate, 1.45-2.16 mmol/L (<2 years), 1.45-1.78 mmol/L (2-12 years), 0.9-1.80 mmol/L (13-16 years), 0.7-1.50 mmol/L (>16 years); magnesium, 0.75-1.0 mmol/L; creatinine, 20-50μmol/L (1 month-2 years), 25-70μmol/L (6-10 years), 40-80μmol/L (10-15 years); 45-90μmol/L (>15 years, females); parathyroid hormone (PTH), 1.6-6.9 pmol/L; potassium 3.50-5.20 mmol/L; calcium to creatinine clearance ratio (CCCR) > 0.01.

Abbreviations: Ca × P, calcium x phosphate product; Ca/P, calcium/phosphate ratio; -, not available.
3-dimensional structures of the inactive and active forms of the CaSR (Protein Data Bank [PDB] accession numbers 7M3E and 7M3F) were used to assess the structural consequences of the CaSR mutation, p.(Phe788Cys) [21]. Molecular modeling was performed using The PyMOL Molecular Graphics System (Version 2.4.0 Schrödinger, LLC). In the inactive CaSR, the wild-type Phe788 was shown to form Pi-Pi interactions with the nearby Phe792 and Phe815 residues, which are located in TM helices 5 and 6, respectively, and these interactions likely stabilize the CaSR in the resting (inactive) state (Fig. 3). The introduction of the mutant Cys788 CaSR residue was predicted to disrupt these Pi-Pi interactions thereby leading to CaSR activation (Fig. 3), and consistent with a diagnosis of ADH1.
The proband’s mother and father did not undergo CASR gene analysis, although they had normal albumin-adjusted serum calcium concentrations of 2.48 mmol/L and 2.31 mmol/L, respectively. These findings indicate that the CASR mutation had likely arisen de novo. Following the diagnosis of ADH1, the calcitriol and calcium dosages were gradually reduced to 0.25 mcg twice daily and 500 mg twice daily, respectively, to achieve an albumin-adjusted serum calcium concentration between 1.90 and 2.10 mmol/L. However, despite stable medication dosages being administered, reported good compliance, and dietitian input to ensure consistent dietary calcium intake, the proband’s serum calcium values remained labile with albumin-adjusted serum calcium concentrations ranging from 1.54 to 2.59 mmol/L (Fig. 1).

Discussion

This case highlights that ADH1 may represent a severe disorder of mineral metabolism characterized by recurrent seizures in infancy, marked hypocalcemia, low or undetectable PTH levels, hypomagnesemia, hyperphosphatemia, a low calcium/phosphate ratio, hypercalciuria, nephrocalcinosis and renal impairment, and also intracerebral calcifications. Such severe clinical consequences have also been reported in other ADH1 patients, who harbored the CaSR missense mutation p.(Phe788Cys), present in the proband [17, 20]. Thus, a previous study showed that the p.(Phe788Cys) mutation is associated with neonatal hypocalcemic seizures, hyperphosphatemia, relative hypercalciuria in infancy, and childhood basal ganglia calcifications [20]. Moreover, this reported study demonstrated that the p.(Phe788Cys) mutation exerts a dominant effect on CaSR function in vitro with cells co-transfected with the wild-type (Phe788) and mutant (Cys788) CaSR showing a similar degree of gain-of-function compared to cells solely expressing the mutant Cys788 CaSR protein [20]. Another study has also shown that the CaSR p.(Phe788Cys) mutation is associated with the development of nephrocalcinosis and basal ganglia calcifications within the first year of life, in addition to causing neonatal hypocalcemic seizures [17].

A notable feature of the present case is the occurrence of highly variable serum calcium concentrations, which caused both hypocalcemic and hypercalcemic episodes (Fig. 1). These serum calcium fluctuations persisted despite a reduction in calcium and calcitriol dosages. Such labile serum calcium concentrations have also been reported in other children and a young adult with severe forms of ADH1 (11) and indicate that germline mutations harbored by these ADH1 patients may impair the effectiveness of the CaSR in maintaining serum calcium at near-constant concentrations.

The proband also had myoclonus, which to the best of our knowledge, has not been reported in ADH1 patients, although it may represent a rare consequence of hypocalcemia due to postsurgical hypoparathyroidism [22]. However, the myoclonic jerks experienced by the proband were not associated with hypocalcemia, and thus the etiology remains to be elucidated. It is possible that the proband’s myoclonus was caused by the bilateral basal ganglia calcifications. Basal ganglia calcifications are a common finding in the general population and are detected incidentally in up to 20% of individuals undergoing brain imaging, with the prevalence increasing with age [23]. Basal ganglia calcifications may be idiopathic or classified into primary monogenic causes, such as primary familial brain calcification, or occur secondary to diseases, such as calcium and phosphate disorders (eg, hypoparathyroidism); brain infections (eg, brucellosis or AIDS); and exposure to toxins (eg, lead or carbon monoxide) [23]. Most cases of basal ganglia calcifications are asymptomatic, as reported by a study of 36 hypoparathyroid patients with basal ganglia calcifications in whom there was no increase in neurological symptoms compared to hypoparathyroid patients without such calcifications [24]. However, some patients with basal ganglia calcifications, particularly due to primary monogenic causes such as mutations of the solute carrier family 20 member 2 (SLC20A2) gene which encodes the Pit-2 inorganic phosphate transporter, develop neurological and/or psychiatric symptoms that include parkinson-
ism, cognitive impairment, depression and/or psychosis [23]. Patients with primary and secondary forms of basal ganglia calcifications have also been reported to develop myoclonus, although this typically occurs in association with other neurological symptoms such as seizures or cognitive dysfunction [25, 26]. In contrast, the ADH1 proband in our study had no additional neurological features, and the underlying cause of her myoclonus remains to be elucidated. Patients with ADH1 and intracerebral calcifications may also develop other neurological features such as cognitive impairment, which has been reported in 2 children with ADH1 and basal ganglia calcifications, one of whom also had extra-pyramidal features such as lead-pipe rigidity [27, 28]. Parkinsonian features have also been reported in 2 ADH1 patients aged > 60 years, who both had extensive intracerebral calcifications [29, 30].

The cause of the intracerebral calcifications in ADH1 patients is unclear and appears unrelated to the severity of hypocalcemia [9]. However, a recent study has reported that low serum calcium/phosphate ratios are associated with basal ganglia calcifications in hypoparathyroid patients [24], and indeed this was found to be the case in the proband (Table 1) in our study. Furthermore, the ADH1 proband was persistently

Figure 3. CaSR mutational analysis of the ADH1 proband. A, Family pedigree with male and females represented by squares and circles, respectively. Affected and unaffected individuals are represented by filled and open symbols, respectively. Arrow indicates the proband. B, The heterozygous T>G transition at nucleotide c.2363 was identified in the proband, which changes a TTC codon to TGC and is predicted to result in a missense amino acid substitution from Phe to Cys at position 788 in the CaSR protein. C, Multiple protein sequence alignment showing evolutionarily conservation of the CaSR Phe788 residue (bold). Gray area indicates conserved CaSR residues. The mutant Cys788 residue is shown in red. D and E, Ribbon diagrams of transmembrane (TM) helices 5 (gray) and 6 (yellow) shown in the inactive CaSR state, and which are derived from published cryo-electron microscopy structures [21]. D, The wild-type Phe788 residue (cyan) is located in TM5 and likely forms Pi-Pi interactions with Phe792 and Phe815, located in TM5 and TM6, respectively. Dashed lines indicate the distance in Angstroms between Phe788 and the Phe792 and Phe815 residues. E, The introduction of a mutant Cys788 residue (green) is predicted to disrupt these Pi-Pi interactions.
hyperphosphatemic as a child (Fig. 1), which may have contributed to the ectopic calcifications. In support of this, extracellular phosphate promotes soft tissue mineralization [31], and mutations of the Pit-2 inorganic phosphate transporter are a major cause of primary familial brain calcification and associated with increased CSF phosphate concentrations and calcium-phosphate deposition within the brain [32, 33].

In summary, this report highlights that myoclonus may be a presenting feature of intracerebral calcifications in ADH1.

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Disclosures
The authors have nothing to disclose.

Data Availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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