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Case Report

A Newborn Male Infant with Seizures, Cyanosis, Bradycardia, and Ischemic Stroke Due to Autosomal Dominant Hypocalcemia with a Missense Mutation in the CaSR Gene: A Case Report

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Abstract

Autosomal dominant hypocalcemia is commonly caused by a gain-of-function mutation in the CaSR gene and inhibits calcium reabsorption in the kidneys by suppressing the secretion of parathyroid hormone. Laboratory findings typically result in hypocalcemia, hyperphosphatemia, hypomagnesemia, hypercalciuria, and low to normal parathyroid hormone. Clinically, patient presentation varies from asymptomatic to life-threatening. We present a full-term baby boy who exhibited episodic right lower extremity stiffening, cyanosis, and bradycardia at day of life 2 with confirmed seizure activity. The patient's course was significant for poor feeding, right vocal cord paralysis, and an ischemic stroke in the posterior division of the right middle cerebral artery. Genetic work-up revealed the unique CaSR heterozygous missense variant mutation c2495T>C (p.lle832Thr), and STX16 gene variation. This patient's sibling also carries the same mutation however is asymptomatic. It is important to monitor these patients for clinical manifestations, as gain-of-function mutations in the *CaSR* gene may carry complications such as nephrocalcinosis, changes in bone mineral density, and a predilection for epilepsy later in life.

MeSH Keywords: *hypocalcemia, seizures, ischemic stroke, hypoparathyroidism familial isolated, CASR protein, human*

Introduction

Extracellular calcium homeostasis is largely regulated by the calcium-sensing receptor (*CaSR*) found in the chief cells of the parathyroid gland and cells lining the kidney tubule [1]. When extracellular calcium binds to *CaSR*, it causes a conformational change leading *CaSR* to couple with other heterotrimeric G proteins, including Gq/11 [2]. When *CaSR*-expressing cells sense alterations in blood calcium levels, the concentration is normalized by regulating parathyroid hormone (PTH) secretion and urinary calcium excretion [3]. Inherited or acquired abnormalities of the *CaSR* gene located on chromosome 3p13.3-21 may cause either hypercalcemia or hypocalcemia depending on whether the mutation is inactivating or activating, respectively [3]. There are several disorders in calcium-sensing arising from inherited or acquired abnormalities [4] (**Table 1**).

Autosomal dominant hypocalcemia (ADH) is caused by a heterozygous activating mutation of the *CaSR* gene [5]. *CaSR* activation suppresses PTH secretion from the parathyroid chief cells and inhibits calcium reabsorption in the renal distal tubule, leading to reduced serum calcium levels [2]. Patients often present with hypocalcemia, hyperphosphatemia, low magnesium levels, low to normal PTH, and hypercalciuria due to activation of *CaSR* found in the renal tubules [5]. Clinically affected individuals are often asymptomatic or experience mild signs and symptoms of hypocalcemia [6]. However, some patients in the more severe spectrum exhibit pronounced neuromuscular irritability and basal ganglia calcification, as well as hypercalciuria that can lead to nephrocalcinosis, nephrolithiasis, and heart failure [7].

Activating mutations of the *CaSR* gene, which is a heterozygous gain-of-function, result in familial or sporadic ADH [8]. Most activating mutations of *CaSR* gene have been reported to be missense mutations [9]. Moon et al. [10] reports a novel activating variant of *CaSR* gene that occurred *de novo* in a Korean neonate. The neonate presented with facial convulsions and muscular contractions in the limbs. Laboratory results show that the neonate has congenital hypoparathyroidism with hypomagnesemia and hypercalciuria. It was found through targeted exome sequencing of the neonate that

the patient has a heterozygous novel variant c.2474A>T(p.Tyr825Phe) in exon 7 of *CaSR* gene. This variant was not found for the neonate's parents which explains that the *CaSR* gene activating variant occurred *de novo*.

Another case report by D'Souza-Li et al.[11] discusses a 21-year-old asymptomatic woman who was tested because three of her sisters and mother all had hypocalcemia. This woman's laboratory results reveal mild hypocalcemia, mild hyperphosphatemia, hypomagnesemia, and low PTH. It was found that the patient, like her siblings, has a familial form of heterozygous mutation leading to the substitution of alanine to threonine in position 835, located in the third extracellular loop of the *CaSR,* which is manifested as ADH.

The two case reports mentioned above demonstrate the varied clinical presentations of activating mutations in the *CaSR* gene where it can manifest as asymptomatic to more severe presentations such as seizures. In our case report, the authors present a case of a newborn male who presented with right lower extremity stiffening, cyanosis, and bradycardia, complicated by an ischemic stroke. Genetic workup for this patient later revealed that it is was ADH due to a heterozygous gene mutation for familial missense variant of the *CaSR* gene c2495T>C (p.lle832Thr) and *STX16* gene variation of unknown significance. This patient's sibling also carries the same mutation for the *CaSR* gene and *STX16*, however, has thus far remained asymptomatic.

Table 1: Various types of CASR gene mutations and associated clinical manifestations [4]

Disease	Type of CASR Gene Mutation	Clinical Manifestation
Autosomal dominant hypocalcemia (Type 1 and Type 2)	Gain-of-function mutation in CASR gene	May be asymptomatic or present with neonatal or childhood seizures
Familial (Benign) hypocalciuric hypercalcemia (FHH)	Autosomal dominant heterozygous loss-of-function mutation leading to inactivation in the CASR gen	Benign clinical course. Lifelong hypercalcemia is usually asymptomatic and is often diagnosed incidentally.
Neonatal severe hyperparathyroidism (NSHPT)	Autosomal recessive loss of function leading to inactivation in the CASR gene	Rare disorder characterized by an aggressive clinical course. Extreme hypercalcemia may lead to hypotonia, bone demineralization, and respiratory distress.

Case Report

A full-term male born to non-consanguineous parents was admitted to the neonatal intensive care unit (NICU) for poor feeding, with absent rooting and poor suck reflex on day of life (DOL) 1. The baby was born at 37+5/7 weeks gestational age via normal spontaneous vaginal delivery to a 26-year-old G2P0101 mother with no significant past medical history. Apgar scores were 4 and 7 (1 minute, 5 minutes) due to poor respiratory effort requiring positive pressure ventilation and poor tone, both resolving within the first 10 minutes of life. All maternal laboratory results were negative for infectious etiology. Family history was significant for a sibling with a rare genetic disorder consisting of two-point mutations in the *STX16* and *CaSR* genes. Parents declined amniocentesis for this baby.

Initial examination on DOL 1 revealed a soft, hoarse cry and uncoordinated sucking. The remainder of the physical examination was unremarkable, and no dysmorphic features were noted. Initial investigations included a capillary blood gas, complete blood count, manual differential, basic metabolic profile (BMP), magnesium and phosphorus levels, of which all were within normal limits including a calcium level of 8.8 mg/dl (range 7.6- 10.4 mg/dl). Flex laryngoscopy was performed, which revealed right vocal cord paralysis. Head ultrasound was unremarkable.

On DOL 2, the baby had a self-resolving episode of right leg stiffening, cyanosis, and bradycardia, followed by two more episodes with stiffening of the right lower extremity and then upper extremity, deviation of eyes to the right, and drooping of right side of mouth. The blood pressure was normal for age. Phenobarbital was started, and sepsis workup was performed. Laboratory results were remarkable for hypocalcemia (Ca = 6.7 mg/dl, normal 7.6-10.4 mg/dl), low albumin (Alb = 2.8g/dL, normal 3.0-3.9g/dL), low PTH (PTH = 1.7pg/ml, normal 18.4-80.1pg/ml) and low Vitamin D (Vit D = 6.6ng/ml, sufficient 20≥ng/ml). The remainder of the comprehensive metabolic panel showed normal results. Coagulation profiles and thrombophilia studies were also done and were within normal limits for age. Echocardiography was unremarkable. Urine calcium levels, pH, renin, and aldosterone levels were not performed. The patient was started on calcium gluconate and Vitamin D.

Continuous video electroencephalogram (EEG) showed multiple seizures arising from the right frontocentral region (lasting on average 1 – 1 ½ minute), not clearly associated with any specific clinical changes. Magnetic resonance imaging (MRI) showed acute to early subacute ischemic stroke in the territory of the posterior division of the right middle cerebral artery (**Figure 1 and 2**). Magnetic resonance angiography (MRA) of the head and neck showed no definitive stenosis or focal occlusion. Repeat MRI prior to discharge showed evolution of the prior infarct, (**Figure 3 and 4**), and though repeat EEG remained abnormal, it did not show further seizure activity. After a 4-week NICU course, the patient was discharged home with phenobarbital, calcitriol, and multivitamins and followed up with neurology, ear nose throat (ENT), endocrinology, speech and swallow services, and Early Intervention.

Due to the known family history significant for a sibling with a rare genetic disorder consisting of two-point mutations in the *STX16* and *CaSR* genes c2495T>C (p.lle832Thr), genetic testing was done for the patient during his stay in the NICU. The patient's microarray revealed no abnormality, though genetic testing revealed using an exome backbone which showed heterozygous gene mutation for familial missense variant of the *CaSR* gene c2495T>C (p.lle832Thr) and *STX16* gene variation of unknown significance. The test was a targeted gene panel for 16 genes associated with hypoparathyroidism. Both sequencing and copy number variant detection was done on the genes. Next-generation sequencing (NGS) and coverage were for >=20x for all exons and the +/- 10 bp of flanking deoxyribonucleic acid (DNA). Any regions with low coverage are backfilled using Sanger sequencing. In addition, all pathogenic, undocumented, and suspect NGS variant calls were also confirmed by Sanger sequencing.

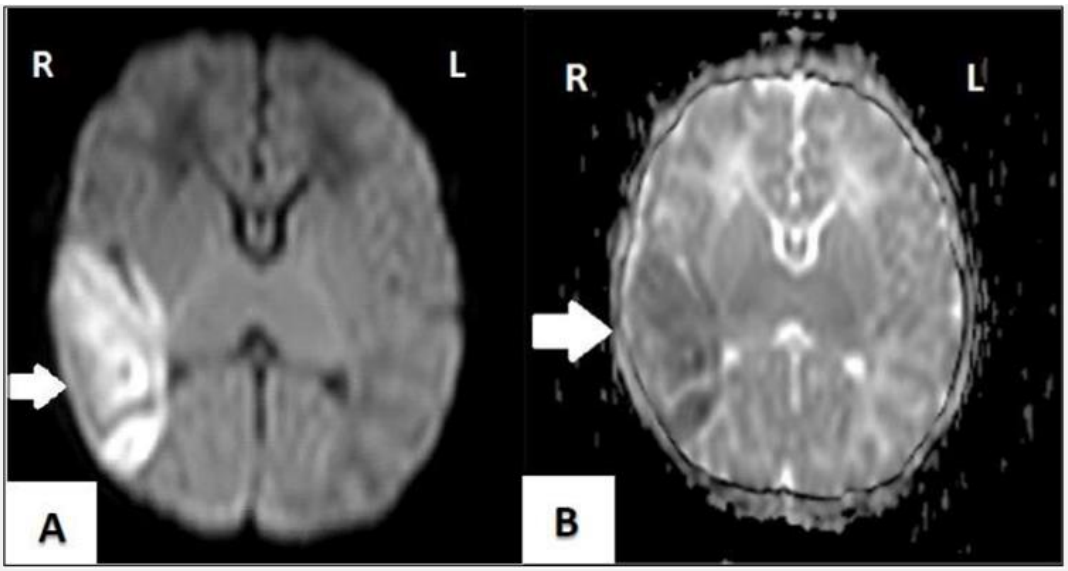

Figure 1A: Diffuse-weighted imaging (DWI) showing a hyperintensity area (arrow) in the territory of the posterior division of the right middle cerebral artery (MCA) involving primarily the temporal lobe, the temporal parietal junction, and the posterior insular cortex, with a small satellite focus in the left corona radiata.
Figure 1B: Apparent diffusion coefficient (ADC) showing a hypointensity (arrow) in the posterior division of right MCA involving predominantly the temporal lobe, the temporal parietal junction, the posterior insular cortex, with a small satellite focus in the left corona radiata.

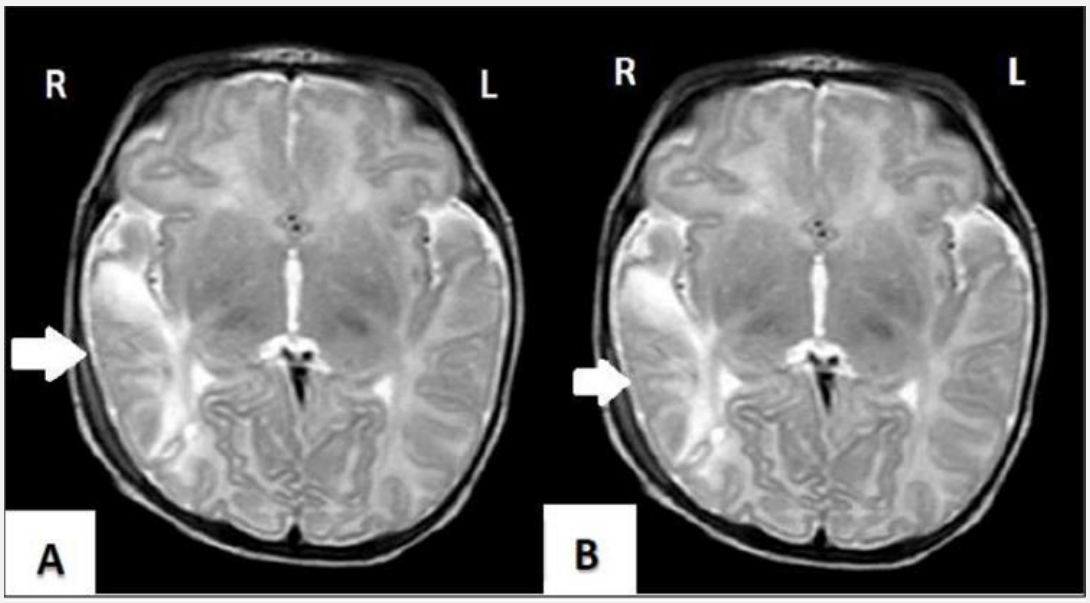

Figure 2A: T1-weighted MRI done before discharge showing a dark cystic formation (arrow) showing the evolution of the prior right MCA infarct, now appearing as a cystic encephalomalacia
Figure 2B: T2-weighted MRI done before discharge showing a bright area of cystic formation (arrow) representing the cystic encephalomalacia

Discussion

The authors emphasize in this case report that patients with heterozygous activating mutations in *CaSR* should be monitored closely as they may present ranging from little to no symptoms to life-threatening complications. In our case, the patient presented with symptoms hypocalcemia, seizure activity, and confirmed stroke in a newborn. Badran et al.[12] also discussed a 1-day-old female (born at 32 weeks gestational age) admitted to the NICU for respiratory distress was found to have neonatal hypocalcemia with normal PTH and high phosphorus, however did not present with any signs or symptoms of hypocalcemia. In contrast, laboratory findings for the patient in this case report revealed true hypoparathyroidism with low serum calcium, low PTH, and low Vitamin D. Although he also showed *STX16* gene variation which is typically manifested as pseudohypoparathyroidism with increased PTH [13], his presentation was consistent with true *CaSR* activating mutation (true hypoparathyroidism with low PTH and hypocalcemia). A sibling of the patient in this case report also has *CaSR* gain-of-function gene mutation with a variant for the *STX16* gene, though presented with a benign course. Different activating mutations in *CaSR* gene can show different representations with incomplete penetrance, explaining the disparity in phenotype for these two siblings [4].

While the etiology of stroke in this newborn remains challenging, there may be a correlation between calcium levels and outcomes in these patients. It is known that calcium plays a role in the cellular and molecular pathways of ischemic neuronal death and has been identified to have cerebroprotective properties in stroke [14]. Moreover, low serum calcium levels have been attributed to poorer outcome, extensive infarction in patients with ischemic stroke, and

large hematoma volumes in adult patients with ICH [15,16]. Though similar research is lacking in newborns, there remains the possibility that a heterozygous activating mutation in *CaSR*, when presenting as hypocalcemia, can further complicate outcomes in patients who experience an underlying stroke. It is important for clinicians to be aware that these children may become symptomatic with seizures and neuromuscular irritability during periods of stress [6]. Many affected patients experience recurrent, unprovoked seizures despite correcting the serum electrolyte abnormalities. This lack of electrolyte disturbance points to clues that calcium-sensing receptor gain of function mutations may have an underlying susceptibility for epilepsy.

Activating *CaSR* gene mutations increases the sensitivity of the receptor to extracellular calcium, resulting in low or inappropriately normal PTH levels and reduced renal calcium absorption. Clinical presentation of an activating mutation in the *CaSR* gene varies from asymptomatic mild hypocalcemia to severe hypocalcemia which may present in neonatal life with seizures. This mutation may also be present later in life with symptoms such as paresthesia, carpopedal spasm or febrile seizures. Approximately 50% of ADH patients have symptomatic hypocalcemia, while >30% have renal and/or intracerebral calcifications [17].

The mainstay treatment of symptomatic ADH patients include active vitamin D metabolites, combined with adequate dietary calcium intake and/or the use of calcium supplementation [17]. Monitoring for hypercalciuria, nephrolithiasis and renal impairment remains important as these are notable side effects of prolonged calcium supplementation. For example, a patient of Greek origin with ADH Type 1 who presented with seizures soon after birth had severe hypocalcemia with normal phosphate, magnesium and 1,25(OH)2D3, while PTH was low [18]. Hypocalcemia remained difficult to correct, and in addition, renal ultrasound at 10 months of age, showed grade 1 nephrocalcinosis, reflecting the relatively high urine calcium concentration despite low serum calcium that may be seen in these patients.

Conclusion

This is a case presentation of hypocalcemia, seizure activity, and confirmed stroke in a newborn with *CaSR* gene gain-of-function mutation. This mutation can carry complications such as nephrocalcinosis, changes in bone mineral density, and a predilection for epilepsy later in life. It is therefore important to monitor patients for clinical manifestations associated with the *CaSR* gain-of-function mutation once a diagnosis has been made, as this mutation may cause little or no symptoms to life-threatening complications.

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Conflicts of Interest

Authors declare no conflicts of interest.

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