Congenital Hyperinsulinism Caused by Novel Homozygous K_{ATP} Channel Gene Variants May Be Linked to Unexplained Neonatal Deaths among Kurdish Consanguineous Families

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Established Facts

- Congenital hyperinsulinism (CHI) is a potentially life-threatening cause of severe hypoglycemia in the neonatal and infant period.
- The incidence of CHI has been estimated to be around 1 in 50,000 in non-consanguineous populations and as high as 1 in 2,500 in areas with a higher rate of consanguinity.
- Certain countries with high rates of consanguinity have a much higher infant and neonatal mortality rate than the rest of the world.

Novel Insights

- Three novel homozygous variants are reported in genes *ABCC8* and *KCNJ11* causing CHI in three Kurdish consanguineous families. Two of these families have a notable history of unexplained neonatal deaths.
- A small but significant percentage of all unexplained neonatal deaths could be due to undiagnosed CHI. Therefore, especially in regions with a high prevalence of consanguinity, undiagnosed CHI can contribute to higher infant and neonatal mortality rates.

Keywords

Congenital hyperinsulinism · K_{ATP} channel variants · *ABCC8* · *KCNJ11* · Consanguinity

Abstract

Introduction: Neonatal hypoglycemia due to congenital hyperinsulinism (CHI) is a potentially life-threatening condition. Biallelic pathogenic variants in K_{ATP} channel subunit

genes (*ABCC8*, *KCNJ11*), causing severe forms of CHI, are more prevalent in regions with a significant rate of consanguinity and may lead to unexplained neonatal deaths. We hypothesized that K_{ATP} channel gene variants are the cause of CHI in three unrelated children from consanguineous

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Kurdish families with histories of four unexplained neonatal deaths with convulsions. **Cases:** (1) A girl presented on the 6th day of life with recurrent hypoglycemic convulsions (blood glucose 2.05 mmol/L, insulin 58 mIU/L, C-peptide 2,242 pmol/L). (2) A girl with severe developmental delay was diagnosed with CHI at 3 years of age (blood glucose 2.78 mmol/L, insulin 8.1 mIU/L, C-peptide 761 pmol/L) despite a history of recurrent hypoglycemia since neonatal age. (3) A girl presented at 3 weeks of age with convulsions and unconsciousness (blood glucose 2.5 mmol/L, insulin 14.6 mIU/L, C-peptide 523 pmol/L). Coding regions of the *ABCC8* and *KCNJ11* genes were tested by Sanger sequencing. Potential variants were evaluated using the American College of Medical Genetics standards. Three novel causative homozygous variants were found – p.Trp514Ter in the *ABCC8* gene (Pt2), and p.Met1Val (Pt1) and p.Tyr26Ter (Pt3) in the *KCNJ11* gene. **Conclusion:** CHI caused by K_{ATP} channel variants was elucidated in three children, providing a highly probable retrospective diagnosis for their deceased siblings. Future lives can be saved by timely diagnosis of CHI when encountering a neonate with unexplained seizures or other signs of recurrent and/or persistent hypoglycemia.

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Introduction

Severe hypoglycemia in the neonatal and infant period is a potentially life-threatening condition. One of the most severe causes of such hypoglycemia is congenital hyperinsulinism (CHI) [1]. CHI is a heterogeneous genetic condition caused by a primary genetic defect of the pancreatic β -cells resulting in uncontrolled insulin secretion [2, 3]. In severe cases, hypoglycemia can occur even right after a child has been fed [1]. Symptoms may be subtle and unspecific, and among them could be symptoms such as seizures, tremulousness, irritability, tachycardia, and hypothermia; therefore, obtaining a correct and timely diagnosis can be challenging [1, 4]. If not treated in time, neonates and infants could die. Repeated significant hypoglycemia interferes with brain development, leading to mental retardation and other long-term neurological sequelae [5, 6].

CHI is caused by variants in genes such as *ABCC8* [7], *KCNJ11* [8], *GLUD1* [9], *HADH1* [10], *GCK* [11], *PGM1* [12], *HK1* [13], *HNF4A* [14], *HNF1A* [15], *SLC16A1* [16], *PMM2* [17], *FOXA2* [18], *INSR* [19], and possibly *UCP2* [20, 21] and *CACNA1D* [22]. In addition, some genetic syndromes such as Beckwith-Wiedemann, Kabuki, and Turner syndromes are associated with hyperinsulinism

[23, 24]. This makes a total of over 15 genes currently associated with CHI.

The most severe forms of CHI are caused by pathogenic variants in genes *ABCC8* and *KCNJ11*, each encoding the SUR1 and Kir6.2 proteins of the ATP-sensitive K^+ (K_{ATP}) channel in the pancreatic β -cell, respectively [23, 24]. The K_{ATP} channel plays a pivotal role in the regulation of insulin secretion. Loss of K_{ATP} channel activity due to *ABCC8* and *KCNJ11* gene variants leads to persistent membrane depolarization and continuous insulin release, regardless of glucose level, thereby causing hyperinsulinism [24]. These variants can either be autosomal recessive or dominant, where recessive biallelic variants usually cause diffuse CHI with a more significant clinical impact [25].

Pharmacological therapies include diazoxide (a K_{ATP} channel inhibitor), octreotide (a short-acting somatostatin analogue), and continuous subcutaneous glucagon in patients who are diazoxide unresponsive (commonly patients having SUR1 and Kir6.2 subunit variants) [26, 27]. Two long-acting somatostatin analogues are currently in use, octreotide long-acting release (octreotide-LAR/Sandostatin-LAR [28]) and Somatuline autogel (lanreotide) [29]. A novel therapeutic option is an inhibitor of the mammalian target of rapamycin (mTOR) signaling pathway sirolimus [30]. Nifedipine, a calcium channel blocker, has also been used with variable success [31].

When conservative medical therapy fails, it is possible to cure focal forms of CHI (distinguished by an ^{18}F -DOPA PET CT scan) with complete surgical resection, while the diffuse form requires a near total pancreatectomy [32, 33].

The incidence of CHI has been estimated to be around 1 in 50,000 in non-consanguineous populations [2, 34, 35]. However, a much higher frequency of 1 in 2,500 was estimated in communities with a higher rate of consanguinity [36].

Timely diagnosis of CHI in the Kurdish region of Iraq could be challenging due to the presence of a less effective health care system and a higher number of home deliveries. All of these factors contribute to the higher neonatal and infant death rates in the region. In 2017, neonatal (NMR) and infant (IMR) mortality rates in Iraq were 17 and 25 per 1,000 live births, respectively [37]. This is in contrast to European countries, which have an average NMR and IMR of 3 and 4, and the United States of America, which has a NMR and IMR of 4 and 6 per 1,000 live births, respectively [37].

We present three children from Kurdish consanguineous families, all diagnosed with CHI at a neonatal age. There is a notable history of unexplained neonatal deaths in two of these families.

Fig. 1. Patient 1's family pedigree. II-2 unknown cause of death, III-1 three deaths with the cause and sex unknown, III-8 death at 4–5 months of age, IV-4 death at 3 days of age with convulsions, IV-5 death at 13 days of age with convulsions, IV-6 proband.

Table 1. Pathogenic gene variants in the 3 patients

Gene	Region	Variant at protein level	Variant at cDNA level	Zygosity	Prediction programs		
					mutation taster	SIFT/Provean	Polyphen2
1 <i>KCNJ11</i> REF SEQ NM_000525.3	Exon 1	p.Met1Val	c.1A>G	Homo	Disease causing	Damaging	Probably damaging
2 <i>ABCC8</i> REF SEQ NM_000352.4	Exon 10	p.Trp514Ter	c.1541G>A	Homo	Disease causing	Deleterious	–
3 <i>KCNJ11</i>	Exon 1	p.Tyr26Ter	c.78C>A	Homo	Disease causing	Neutral	–

Case Reports

Patient 1

A female infant was born full term, with a birth weight estimated above 4 kg (large for gestational age, standard deviation [SD] over +2.0 [38]) and unknown length, to healthy Kurdish parents who are first cousins (Fig. 1). During the neonatal period, she presented having recurrent convulsions due to hypoglycemia. She was suspected of having hyperinsulinism based on high random insulin level (basal insulin 205 mIU/L [normal range 2.6–24.9], C-peptide 4,701 pmol/L) and was therefore put on short-acting octreotide due to the lack of diazoxide in this region. At 4 months of age, when a partial pancreatectomy was being considered, she was referred to a pediatric endocrinologist, where blood glucose during

critical sample was 2.05 mmol/L (37 mg/dL), with high insulin 58 mIU/L and C-peptide 2,242 pmol/L, and inappropriately low cortisol of 8.15 nmol/L (normal range 171–536) and ACTH of 4.65 ng/L (normal range 7.2–63.6). An ACTH stimulation test (Synacthen test with i.m. depot Synacthen) helped to exclude primary adrenal insufficiency with stimulated cortisol of 943 nmol/L.

The patients' and their respective family members' genomic DNA was extracted from peripheral blood (obtained with informed consent) using QIAmp DNA Blood Mini (Qiagen, Hilden, Germany). In some family members, DNA was isolated from saliva using Oragene DNA OG-500 (DNA Genotek, Ontario, Canada). DNA was analyzed using methods of direct Sanger sequencing by sequencer ABI 3130xl. The complete coding regions and intron-exon boundaries of genes *ABCC8* and *KCNJ11* were analyzed

Fig. 2. Patient 2's family pedigree. I-1 and I-2 distant relatives, II-1 and II-2 distant relatives, II-2 diabetes mellitus, II-4 death at 5 years, II-5 death due to war, III-2 and III-4 death due to an accident, III-5 death due to war, IV-3 gestational diabetes mellitus, III-9 five male infants died of an unknown cause, V-6 death at 1 day of life with convulsions and cyanosis, V-7 death at 1 day of life with convulsions and cyanosis, V-8 proband.

as two of the most common causes of CHI. Results were verified using the program Mutation Surveyor. Each possibly pathogenic variant was then evaluated according to the American College of Medical Genetics and Genomics standards and guidelines.

A novel homozygous pathogenic variant p.Met1Val (c.1A>G) was found in gene *KCNJ11* (Table 1). Her parents and one healthy sibling tested heterozygous for the same variant (Fig. 1).

After genetic diagnosis, she was started on octreotide-LAR. Three doses were given (1.2 mg subcutaneously per month), after which hypoglycemia resolved. During this 3-month period, she was given short-acting octreotide 40 µg/day as well. Since her hypoglycemia was difficult to control and she showed a poor cortisol response during hypoglycemia, as a temporary solution, hydrocortisone 15 mg per surface area was added to the treatment regimen for a period of 1 month (three doses a day).

At the age of 13 months (length 75 cm [−0.4 SD], weight 11.3 kg [+1.5 SD]), her dose of long-acting octreotide was increased to 4.6 mg per month. Her HbA1c was 31 mmol/mol (DCCT – 5.0%), suggesting that she maintained her mean blood glucose level within the normal range. Her growth and psychomotor development are normal.

Notably, the patient has a history of two siblings, female and male, who died on the 3rd day and 13th day of life, respectively, with generalized seizures. The cause of death was not properly elucidated.

Patient 2

A female infant was born in a Kurdish consanguineous family (Fig. 2) to a mother with a history of gestational diabetes in all her pregnancies. She was born preterm, at the 35th week of gestation, with a birth weight of 3.3 kg (large for gestational age, +2.0 SD) [39].

From 4 days of age, she had recurrent symptomatic hypoglycemia but was only treated with frequent feeding and glucose, during which she had several severe hypoglycemic episodes. At the age of 3 years and 8 months, she was referred to a pediatric endocrinologist, where a critical sample was obtained with a blood glucose level of 2.8 mmol (50 mg/dL), inappropriately high insulin level of 8.1 mIU/L, and C-peptide level of 761 pmol/L. At the time of hypoglycemia, cortisol was appropriately elevated to 893 nmol/L; thereafter, the diagnosis of hyperinsulinemic hypoglycemia was

Fig. 3. Patient 3's family pedigree. II-2, -3, -4, -6 died in middle to old age for unknown reasons, II-7 and II-8 distant relatives, II-7 myocardial infarction, III-6 death at 1 year of age due to fever, III-7 unknown cause of death in 2 males, III-8 death at 5 years due to unknown cause, IV-1 8 years old, IV-2 5 years old, IV-3 3 years old, V-5 proband, 2.5 years old, IV-6 1 year old.

made. At this stage, she already had severe developmental delay. At her current age of 7 years, she does not speak and is unable to walk, partially due to muscle spasticity.

After her clinical diagnosis, she was put on corn starch and nifedipine 0.2 mg/kg/day, due to the lack of diazoxide in this region. Nevertheless, she continued to have further episodes of hypoglycemia (blood glucose around 2.7 mmol/L, 50 mg/dL), which improved with the introduction of uncooked starch to her diet.

Genetic testing using methods described above revealed that she is homozygous for a novel nonsense pathogenic variant in the *ABCC8* gene p.Trp514Ter (c.1541G>A) (Table 1). Her parents tested heterozygous for the same variant (Fig. 2). After genetic diagnosis and due to the uncertain effect of nifedipine in the management of CHI, her medication was then changed to octreotide-LAR (a lower dose of 2.5 mg, due to hypoglycemic events being in the range of 2.7–3.3 mmol/L, 50–60 mg/dL) and she is doing well clinically with no further hypoglycemic episodes.

It is important to note that this patient's healthy consanguineous parents have three other healthy children; however, they also

have a history of two spontaneous abortions and two children who died 1 day after birth having cyanosis and convulsions (as described by their parents), these children were born at home and not taken to hospital even after they died. Their family history also includes five male infants, siblings of the patient's father, who died from an unknown cause.

Patient 3

A female baby was born full term (gestational age 39 weeks + 4 days, birth weight 3.0 kg – appropriate for gestational age, 0.0 SD) to healthy consanguineous Kurdish parents with three other healthy children (Fig. 3). She presented with hypoglycemia at 3 weeks of life causing convulsions and loss of consciousness. She was discharged from a local hospital on recommended frequent feeds, uncooked starch, and glucagon injections if needed, with no definitive diagnosis.

At 3 months of age, she was referred to the pediatric endocrinologist due to frequent episodes of symptomatic hypoglycemia and she was admitted to the hospital for further investigation. Af-

ter 4 h of fasting, her blood glucose came down to 2.5 mmol/L (45 mg/dL) and a critical sample was obtained. The insulin level (14.6 mIU/L) was not suppressed at the time of hypoglycemia, C-peptide was 523 pmol/L, cortisol 220 nmol/L, and ketone bodies were absent in urine. She was put on nifedipine 0.23 mg/kg/day, on which there was no improvement. When diazoxide was made available to this patient, her treatment was then changed to diazoxide with no noticeable improvement either.

Parents then took her to India, where an ^{18}F -DOPA PET CT scan was carried out revealing a diffuse form of CHI. She was put on a combined therapy of diazoxide and octreotide. Since she responded to her first dose of octreotide, at 6 months of age (back in Iraq), her treatment with diazoxide was tapered off (due to development of hirsutism and lack of response) and short-acting octreotide was given three times a day.

Genetic analysis revealed a novel homozygous nonsense pathogenic variant in the *KCNJ11* gene, p.Tyr26Ter (c.78C>A) (Table 1). Her parents tested heterozygous for the same variant and her healthy siblings tested heterozygous or negative (Fig. 3). After genetic diagnosis was confirmed, octreotide-LAR 2 mg per month was started. Short-acting octreotide was stopped 1 month after starting long-acting octreotide. Currently, at the age of 2.5 years, she is doing well with a dose of 3 mg per month of long-acting octreotide. Her HbA1c is 34 mmol/mol (DCCT – 5.3%).

Discussion

Consanguineous marriages are common in some countries including the Kurdish region of Iraq. The increased frequency of homozygous genotypes in children from such marriages allows less common alleles to manifest as homozygous; thus, descendants of consanguineous parents have a higher frequency of recessive genetic conditions than those of unrelated parents. If a single-molecule mechanism is the pathophysiological mechanism of the individual conditions, consanguineous families provide the best chances to successfully encounter novel genes and variants.

The cause of CHI varies among populations depending on the percentage of consanguinity. For example, in Europe, where consanguinity is quite rare, CHI is predominantly caused by autosomal dominant mode of inheritance, which leads to generally milder patient phenotypes [34]. In consanguineous populations, autosomal recessive variants prevail, causing more severe CHI [23, 24]. Monoallelic CHI is more likely to respond to diazoxide therapy, whereas recessive disease most often requires therapy with octreotide [25]. Timely identification of the genetic background helps clinicians decide on the type of treatment. However, genetic diagnosis is not often available in certain countries. This along with limited availability of diazoxide in such regions could be the cause of some CHI patients having to undergo a possibly unnecessary near total pancreatectomy.

In all three of our families, pathogenic novel homozygous variants were found in K_{ATP} channel genes. All identified variants were not listed in the GnomAD database and were described as pathogenic by the in silico prediction programs Mutation Taster, SIFT, and PolyPhen-2. The American College of Medical Genetics and Genomics standards and guidelines classified these variants as being pathogenic (Ia) (Table 1).

Variant 1 (p.Met1Val in gene *KCNJ11*) causes the loss of the initiating methionine and changes the Kozak sequence. It could be presumed that this protein is shortened or not coded at all. The two other variants (p.Trp514Ter in gene *ABCC8* and p.Tyr26Ter in gene *KCNJ11*) cause a stop signal leading to the premature termination of protein synthesis of the SUR1 protein from amino acid 514 and the Kir6.2 protein from amino acid 26, respectively, which results in a shorter protein with lost or changed function.

All three children come from heterozygous asymptomatic parents and have asymptomatic siblings who tested negative or heterozygous. The above factors strongly support the pathogenicity of these variants.

Most children with CHI, like in our three families, are born to healthy parents. Two of our families, notably, had a history of unexplained neonatal deaths. Family 1 reported two children dying on the 3rd and 13th day of life with convulsions (Fig. 1). Family 2's description of two newborns dying with convulsions and cyanosis, both on the first day of life, could be quite indicative of hypoglycemia (Fig. 2).

It is highly probable that the infant deaths in these families could be caused by undiagnosed hyperinsulinism and that these infants were also born homozygous for the same pathogenic variants as found in our patients, respectively. In addition, the family history of Family 2 (Fig. 2) included five male infants, siblings of the patient's father, who died from an unknown cause. However, the possibility of the same mutation causing these deaths was ruled out as the paternal grandmother tested negative for the same *ABCC8* variant. The cause of these deaths could only be speculated.

In Family 3, no infant deaths were reported (Fig. 3), all children born to the family were heterozygous or negative until the birth of our patient. However, if CHI had not been correctly considered at the time of presentation of hypoglycemia symptoms, this child may have had a worse outcome as well.

A prospective study from Iran revealed a mortality rate of 53.8% out of 14,000 hypoglycemic infants who were evaluated with regard to blood glucose level at the first 24 h of life over a 2-year period. Prematurity (61.5%) was the leading cause of death. A percentage of 1.9% of these deaths were reportedly due to CHI [40]. Whereas data on the IMR

in neonates due to hypoglycemia are otherwise not available, it could be speculated that even a higher proportion of neonatal deaths worldwide could be due to CHI.

All three patients are now successfully managed with monthly doses of long-acting octreotide; there are currently no episodes of hypoglycemia or lack of consciousness.

Due to the fact that pathogenic homogenous variants in K_{ATP} channel genes were found in all these families, diagnosing CHI, it is highly probable that these neonatal deaths, described with the presence of convulsions, could indeed have been due to hypoglycemia. Such undiagnosed cases, unfortunately, may be classified as unexplained neonatal deaths in such regions due to home births, not taking children to the hospital, lack of facilities and of genetic counseling. There being a lack of any other publication regarding CHI stemming from the Kurdistan region to our knowledge, our findings provide a glimpse into the possibly high incidence of CHI and neonatal deaths that could be prevented if diagnosed in time. This translates to the same necessity in all regions with prevalent consanguinity. These cases show the importance of considering hyperinsulinism as a possible diagnosis when encountering a child with recurrent and persistent hypoglycemia and/or seizures in order to save future lives.

Among the clear limitations of our study belong factors such as the lack of all complete clinical data from primary care physicians, unreliable birth size parameters due to home births, and limited reliability of laboratory results. A significant limitation is that the pathogenicity of the elucidated novel variants was assessed and deemed causative only by the clinical phenotype, segregation in the family, and prediction programs. Further functional assessment of these variants is not available. Genetic testing in the deceased siblings of these patients was not possible.

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Statement of Ethics

Our patients' parents gave informed consent for the genetic testing reported in this paper and for the publication of related data. This study was approved by the Ethics Committee at the 2nd Faculty of Medicine, Charles University in Prague. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.L. and S.P. designed the study. S.A.A. did the genetic testing for most patients and family members and coordinated the study. S.A.A. and K.R. wrote the manuscript. T.H.T. referred the patients, provided their clinical information, and reviewed the manuscript. P.K. provided insight on variant analysis. All authors contributed to the discussion and reviewed or edited the manuscript.

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