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CONGENITAL HYPERINSULINISM: FIRST CASE REPORTS FROM THE REPUBLIC OF ARMENIA.

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Abstract

Congenital hyperinsulinism is a rare disorder of insulin-producingbeta-cells affecting 1 in 50,000 newborns. Individuals with congenital hyperinsulinism have frequent episodes of hypoglycemia due to inappropritate plasma insulin levels for the blood glucose level. Some forms of congenital hyperinsulinism-resolve spontaneously and are transient, whereas others persist for longer and are considered permanent. The main risk groups for developing transienthyperinsulinaemic hypoglycemia aresmall for gestational age newborns, those subjected to hypoxic fetal distress and those born to mothers with diabetes mellitus.

At least 14 further genes have to harbor causative mutations in individuals with congenital hyperinsulinism, including the Glucokinase gene which encodes the "glucose sensor" for the beta cells. These dominantly acting mutations increase the enzymatic activity of Glucokinase gene and often arise spontaneously.

The clinical severity of congenital hyperinsulinism varies widely among patients, even among the individuals with the same genetic aetiology. Not all children with congenital hyperinsulinism experience hypoglycemia right after birth or during the first month of life (60-65%). Almost 30% of affected individuals develop hypoglycemic episodes during infancy. The main clinical symptoms are irritability, sleepiness, lethargy, hunger and tachycardia, as wellas weakness, tiredness, confusion, tachycardia and aggressive behaviours. More severe symptoms, such as seizure and coma, occur after prolonged hypoglycemia or due to a rapid drop of blood glucose level. Recurrent moderate hypoglycaemias, as well as severe hypoglycemic episodes may cause brain injury and cognitive impairment in the longterm.With early treatment and careful prevention of hypoglycemic episodes the brain damage can be prevented.

There are no previous reports of congenital hyperinsulinism from Armenia.In this manuscript we describe 3 cases of congenital hyperinsulinism from Armenia who presented with different clinical phenotypes and report the results of genetic testing. Current cases are the first reports from Armenia, and can serve as a base for increase awareness of congenital hyperinsulinism in the relevant country.

Keywords: *congenital hyperinsulinism, hypoglycemia, glucokinase mutation, diazoxide*

Introduction

Presentation of cases:

Case 1. A 5-month-old girl was referred to the Endocrinology department of "Muratsan" University Hospital with a diagnosis of epilepsy and underwent an EEG and a brain MRI scan and started on anti-

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epileptic therapy.However, further investigations confirmed that the seizures were due tosevere hypoglycemic episodes (blood glucose level ranged 0.2-0.9*mmol/l*). At the admission the blood glucose level was 1.1*mmol/l* and the simultaneous serum insulin was 7.4*mU/l*, confirming the biochemical diagnosis of hyperinsulinemic hypoglycemia (with negative ketone bodies in the urine). There wasno any syndromic and dysmorphic features.The family history was unremarkable. She was commenced on diazoxide (maximum dose of 13.5 *mg/kg/day*) and her intravenous glucose infusion was weaned off. On the diazoxide she was able to maintain her blood glucose levels between 3.3-4.9*mmol/l.* Feeding plan of low-carb diet was performed with fasting intervals not longer than 4 hours and included overnight boluses. Molecular genetic analysis of *KCNJ11*, *ABCC8*, *GLUD1*, *GCK*, *HADH*, *HNF4A*, *INSR*, *KDM6A*, *KMT2D*, *SLC16A1*, *CACNA1D*, *PMM2*, *TRMT10A* and *HNF1A (CHI known genetic panel)*was performed by targeted next generation sequencing, however no mutations were identified. The patient is currently2 years old with clinical features of marked hirsutism as a side effect of diazoxide and development delay with delay in gross motor skills.

Case 2. The male Caucasian child was admitted to the Endocrinology Department of "Muratsan" University Hospital at the age of 2 yearswith hypoglycemia (blood glucose level of 2.5*mmol/l*). In the past history he had two episodes of remarkable general weakness and fatigue, which were transient and did not require hospitalization.The patient was started on diazoxide,and the lowest-effective dose was titrated as 13*mg/kg/day*.Molecular genetic analysis of 14 known hyperinsulinism genes was performed which identified anovel mosaic likely disease-causing variantin *GCK*. The found mutation of *GCK*is described as NM_000162.4:c.1340G>T p.(Arg447Leu) located Chr7:g.44184793. The mutation was present at approximately 30% in the child's leukocyte DNA. Testing of the unaffected parents did not detect the mutation, confirming that the mutation had arisen *de novo* in the child.The child is 3 years old now and is currently on diazoxide (11*mg/kg/day*) and has severehirsutism. Despite being on this dose of diazoxide he still has occasional episodes of hypoglycemia due to family incompliance to the prescribed treatment. Developmentally he seems appropriate.

Case 3. An8.5-months oldmale was admitted to the ICU department of "Arabkir" Medical Center with severe weakness and a blood glucose level of 1.33*mmol/l*.In his previous history he had seizures (no blood glucose level was measured)but did not require hospitalization.An intravenous glucose infusionwas started immediately: the averagerate was 15-17*mg/kg/min*.Molecular genetic analysis of the *CHI known genetic panel* was performed by targeted next generation sequencing, however no mutations were identified. The child is 1 years old now and takes diazoxide (7.5-8*mg/kg/day*) with positive response and appropriate glycaemic control.

The summary of phenotype-genotype peculiarities of presented cases are described in the Table 1.

Informed consent was obtained from the parents for the discription of case reports.

Discussion.

There is a great variability in clinical findings and severity in patients presenting with CHI. Differences are found between age of clinical presen-

Table 1.

Clinical findings, medication dosage and laboratory results of currently reported patients with hyperinsulinemic hypoglycemia.

Variables	Patient		
	1	2	3
Birth weight (*kg*)	3.1	4.7	3.690
Gestation (weeks)	39	40	40
Age at presentation	5 months	2 years	9 months
Seizure	+	-	+
BMI (kg/m^2)	13.5	21	18.4
Glucose at admission (*mmol/l*)	1.1	2.5	1.33
HbA1c (%) at presentation	2.9	3.1	3.0
HbA1c %) second measurement	3.5	4.1	4.2
Insulin level at the admission (NR=2.6-24.9*mU/ml*)	7.74	121.3	13.2
Diazoxide dose at the diagnosis (*mg/kg/day*)	13.5	13.3	10.5
Diazoxide-sensitive	+	+	+
Genetic testing	No known mutation	Mosaic mutation in *GCK*	No known mutation

tation, severity of hypoglycemia and clinical symptoms, and the dose of diazoxide required for the management of the disease in both thosewith and without known genetic mutations.There is no strong genotype-phenotype correlation in many patients with CHI. Common specific symptoms for genetically "negative" but diazoxide-sensitive patients are not described, that could be pathognomonic for differential diagnosis and prognosis.As shown in theTable 1we present a case with mild clinical symptoms ina child with a confirmed *GCK* mutation, as well as two cases of CHI, having no known genetic mutations.Further research is needed to identify new molecular mechanisms of diazoxide responsive CHI.

The 2nd child is mosaic for a novel *GCK* missense variant, p.(Arg447Leu), the level of mosaicism in leukocyte DNA was at least 30%, consistent with a post-zygotic variant. This activating variant of *GCK* mutation is likely to be disease-causing according tothe American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines (Evidence code-level), published by Richard et al, 2015[*Richards S et al., 2011*]. Based on updated ACGS Practice Guideline, 2020 the found p.(Arg447Leu)variant has not been reported in the gnomAD database (PM2_Moderate), is not present in either parent and is characterized as *de no*vo variant(PM6_Moderate) [*Ellard S et al., 2020*]. The GCK gene has a low rate of benign missense variation, which is evidenced by a significant ExAC constraint score (PP2_Supporting). It is given, that the p.Arg447 residue is conserved across 20 species and has a consurf scoreof 9. The p.(Arg447Leu) variant is predicted by SIFT, PolyPhen and AlignGVGD to have adeleterious effect on protein function (PP3_Supporting). Summarizing the above mentioned the found mutation is likely pathogenic for the currently described child. The probability of future risk of having an affected child in this patient depends on the level of mosaicism in germ cells butcould be up to 50%.

WHAT IS NEW?

- We introduce first case reports of congenital hyperinsulinism from the Republic of Armenia.
- We report clinically milder and later-onset clinical manifestationsin a patient with a *GCK* missense mutation, compared with the patients without a known mutation. The patient without known genetic mutation developed hypoglycemia earlier (at the age of 5 months) and more severe (with seizures and glucose =1.1mmol/l) than the the child with *GCK* mutation, who presented with hypoglycemic clinical symptoms at the age of 2 years with less severity, without seizures.
- The first child required almost the same or even higher starting dose of diazoxide and now has significant developmental delay, comparing to the second and third children.

REFERENCES

1. *Arya VB, Flanagan SE, Kumaran A, Shield JP, Ellard S, Hussain K, et al. (2013)*. Clinical and molecular characterization of hyperinsulinaemic hypoglycemia in infants born small-for-gestational age. Arch Dis Child Fetal Neonatal Ed.2013;98:F356-8.
2. *Ellard S, Baple EL, Callaway A, Berry I, Forrester N, Turnbull C, et al. (2020)*. ACGS best practice guideleined for variant classififcation in rare disease 2020 (https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf)
3. *Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. (2013)*. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. Eur J Endocrinol. 2013;168:557-564.
4. *Languren G, Montiel T, Julio-Amilpas A, Massieu L. (2013)*. Neuronal damage and cognitive impairment associated with hypoglycemia: An integrated view. Neurochem Int. 2013;63(4):331-343. doi:10.1016/j.neuint.2013.06.018
5. *Laver TW, Wakeling MN, Hua JHY, Houghton JAL, Hussain K, Ellard S, Flanagan SE. (2018)*. Comprehensive screening shows that mutations in the known syndromic genes are rare in infants presenting with hyperinsulinaemic hypoglycaemia. Clin Endocrinol (Oxf). 2018 Nov; 89(5), 621-627.

6. *Loechner KJ, Akrouh A, Kurata HT, Dionisi-Vici C, Maiorana A, Pizzoferro M, et al. (2011)*. Congenital hyperinsulinism and glucose hypersensitivity in homozygous and heterozygous carriers of Kir6.2 (KCNJ11) mutation V290M mutation: K(ATP) channel inactivation mechanism and clinical management. Diabetes.2011;60(1):209-217.
7. *Lord K, De Leon-Crutchlow DD. (2019).* Neurodevelopmental outcomes. In: Congenital Hyperinsulinism: A Practical Guide to Diagnosis and Management, De Leon-Crutchlow DD, Stanley CA (Eds), Humana Press, 2019. p.155.
8. *Lord K, Dzata E, Snider KE, Gallagher PR, De Leon DD.(2013.)* Clinical presentation and management of children with diffuse and focal hyperinsulinism: a review of 223 cases. J Clin Endocrinol Metab.2013;98(11):E1786-9.
9. *Ludwig A, Ziegenhorn K, Empting S, Meissner T, Marquard J, Holl R, et al. (2011)*. Glucose metabolism and neurological outcome in congenital hyperinsulinism. Semin Pediatr Surg.2011;20:45-49.
10. *Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. (2003).* Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol. 2003;149(1), 43-51.
11. *Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V, et al. (2001).* Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics.2001;107:476-9.
12. *Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. (2015).* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med.2015 May;17(5):405-24.
13. *Rosenfeld E, Ganguly A, De Leon DD. (2019).* Congenital hyperinsulinism disorders: Genetic and clinical characteristics. Am J Med Genet C Semin Med Genet. 2019 Dec;181(4):682-692.
14. *Rozenkova K, Guemes M, Shah P, Hussain K. (2015)*. The diagnosis and management of hyperinsulinaemic hypoglycemia. J Clin Res Pediatr Endocrinol.2015;7(2):86-97.
15. *Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA. (2005).* Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. J Pediatr Nurs.2005;20(2):109-18.
16. *Yorifuji T. (2014)*. Congenital hyperinsulinism: current status and future perspectives. Ann PediatrEndocrinolMetab.2014;19(2):57-68.

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