folia medica

Folia Medica 63(5):805-8
DOI: 10.3897/folmed.63.e55696

Case Report

Familial Hyperinsulinaemic Hypoglycaemia with Epileptic Syndrome, Cognitive Impairment and Detected Mutation of the ABCC 8 (SUR1) Gene: a Case Report

Ana Shopova, Silvia Shopova, Irina Stefanova, Rumyana Kuzmanova

Department of Neurology, St Naum University Hospital of Neurology and Psychiatry, Medical University of Sofia, Sofia, Bulgaria

Corresponding author: Ana Shopova, Department of Neurology, St Naum University Hospital of Neurology and Psychiatry, Medical University of Sofia, Sofia, Bulgaria; E-mail: ani_veskova@abv.bg; Tel.: +359 887 338 186

Received: 22 June 2020 ♦ **Accepted:** 22 Mar 2021 ♦ **Published:** 31 Oct 2021

Citation: Shopova A, Shopova S, Stefanova I, Kuzmanova R. Familial hyperinsulinaemic hypoglycaemia with epileptic syndrome, cognitive impairment and detected mutation of the ABCC 8 (SUR1) gene: a case report. Folia Med (Plovdiv) 2021;63(5):805-8. doi: 10.3897/folmed.63.e55696.

Abstract

Hyperinsulinaemic hypoglycaemia (HH) occurs as a consequence of unregulated insulin secretion from pancreatic beta cells. It is the most common cause of severe and prolonged hypoglycemia in newborns. HH is a major risk factor for brain damage and subsequent neurological disability, which is why the identification, rapid diagnosis, and timely treatment of patients with HH are essential for the prevention of brain damage. The present case gives a brief description of a patient with congenital HH with an established mutation in the ABCC8 gene encoding the SUR1 subunit of the K-ATP channel. The genealogical tree, the clinical picture, the diagnostic cascade, the neurological consequences and their development in dynamics are considered, with special emphasis on the epileptic syndrome and mental status. Advances in molecular genetics, radiological imaging techniques, conservative treatment, or laparoscopic surgery may completely change the clinical approach to children with severe congenital forms of HH.

Keywords

congenital hyperinsulinaemic hypoglycaemia, mental retardation, symptomatic epilepsy

INTRODUCTION

Hyperinsulinaemic hypoglycaemia (HH) is a consequence of unregulated secretion of insulin from pancreatic beta cells. In newborns, it is the most common cause of severe and prolonged hypoglycaemia. The brain requires a continuous supply of glucose from the blood, which provides cellular fuel for its metabolism. About 60% of dietary glucose is used in the liver or stored as a reserve in the form of glycogen. About 25% of glucose is digested by the brain and some other tissues (erythrocytes, kidneys, intestinal mucosae, and the Langerhans islands of the pancreas), in which glucose enters without the need of insulin. The remaining 15% enter the skeletal muscle and fat depots through transport systems dependent on insulin and adenosine-diphosphate (ADP). In normal beta cells, increased glucose metabolism raises the ratio of adenosine-triphosphate (ATP) to ADP and closes the K-ATP channels. As a result, the membranes are depolarised, the voltage-dependent calcium channels (VDCCs) open, and intracellular calcium (Ca^{2+}) is increased, causing the release of insulin. With the persistent hyperinsulinaemic hypoglycaemia in early childhood (PHHI), the K-ATP channels are inactive, the cell membranes are depolarized and VDCCs are spontaneously active. The increase in Ca^{2+} leads to continuous release of insulin. Sulphonylurea

closes the K-ATP channels and stimulates insulin secretion, while diazoxide opens the channels and inhibits it.[1,2] The transient decrease of blood sugar causes disturbances in brain function, and more prolonged and severe hypoglycaemia leads to hypoglycaemic seizures, coma, and brain death. HH can be due either to genetic reasons (congenital) or be secondary to certain risk factors. The molecular mechanisms leading to HH include defects in the key genes regulating the secretion of insulin from the β-cells. Under normal physiological conditions, the β-cells of the pancreas secrete insulin to support the fasting blood glucose levels in the range of 3.5 – 5.5 mmol/L. In HH, this precise adjustment of insulin secretion is disrupted, so insulin remains secreted in the presence of hypoglycaemia. At a molecular level, genetic abnormalities in nine different genes *(ABCC8, KCNJ11, GLUD1, GCK, HNF4A, HNF1A, SLC16A1, UCP2* and *HADH)* have been identified to cause congenital hyperinsulinism. Autosomal recessive and dominant mutations in *ABCC8/KCNJ11* are the commonest cause of medically unresponsive congenital hyperinsulinism.[3] Perinatal stress, intrauterine growth retardation, diabetes mellitus in the mother, and a large number of developmental syndromes are also associated with the HH in the neonatal period. In older children and insulinoma in adults, the syndrome of non-insulinoma pancreatic hypoglycaemia and postbariatric surgery are proven causes of HH.[4,5]

CASE REPORT

We present a patient with a congenital familial hyperinsulinaemic hypoglycaemia (FHH), with an established mutation in the ABCC8 gene, encoding sulfonylurea receptor 1 (SUR1) of the K-ATP channel. The genealogical tree, the clinical picture, the diagnostic cascade, the neurological consequences and their development in dynamics, with a particular emphasis on the epileptic syndrome and the mental status, are considered.

Medical history: A woman of 24, with the onset of epileptic seizures at the age of 40 days, flowing with shaking of the head, frequent flashing, lips sacking, flexion-extension in the limbs, followed by loss of consciousness in minutes, with a frequency of more than 10 relapses a day. In early childhood, "West Syndrome" was diagnosed. Antiepileptic treatment was initiated, although hypoglycaemia of up to 1.9 mmol/L was detected repeatedly in seizures. In this period, the blood glucose profile was not regularly monitored. Initially, antiepileptic therapy was conducted with phenobarbital, carbamazepine, clonazepam, vigabatrin, ACTH - as mono- and polytherapy. The patient was seven years without seizures. At 12 years of age, seizures with bilateral tonic-clonic seizures started, achieving drowsiness and vomiting at normal blood glucose levels were added, measured immediately after a seizure. Against the background of treatment with Depakin Chrono 900 mg/day and Lamictal 100 mg/day average seizure frequency became once in a month.

Genealogical examination and genetic diagnosis: The patient was born into a inbreeding data family. The younger sister of the proband was with clinical manifestations of hypoglycaemia in the first hours after childbirth, and due to this heredity was suspected. A genetic study of the sibling was conducted as for mutations, in charge of FHH.*

In the patient's sibling, an analysis according to PCR-direct sequencing method of two genes was conducted: SUR1 (ABCC8) and KCNJ11. In the testing of SUR1 (ABCC8), exons 1-39 was found that a homozygote for a missense mutation R1215W (R1215W/R1215W) in exon 29 of the ABCC8 gene. The patient was confirmed as a homozygote for the same mutation, and in the parents, heterozygosity was established for ABCC8 gene R1215W (R1215W/N) ***(Fig. 1).***

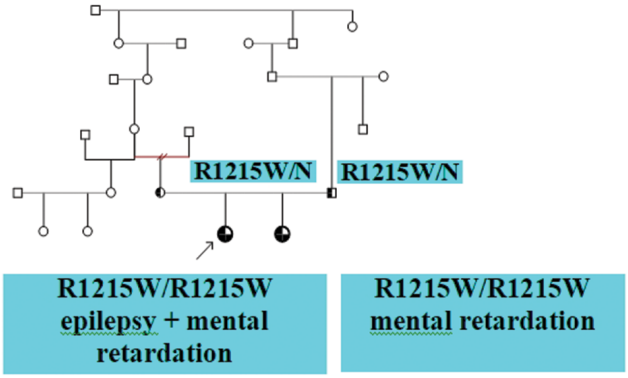

Figure 1. Genealogical tree presenting genetic diagnosis and clinical manifestations. R1215W/N heterozygous carrier for ABCC8 gene – proband's parents; R1215W/R1215W homozygous carrier for ABCC8 gene with clinical manifestation - proband and sibling; *proband's father is grandmother's second cousin of mother's line of the proband.

Tests conducted: Blood sugar profile: The patient has a good control of the blood sugar level at present; Serum levels of anticonvulsants: VPA – 657.2 μmol/l, lamotrigine – 41.7 mmol/l.

Over the years, the patient has undergone periodically EEG tests mainly with data for nonspecific minor changes, with poorly organized main activity for this age.

From the CT of the cerebrum ***(Fig. 2)****, non-compliant for this age cerebral cortical atrophic changes are visualized.*

Neuropsychological examination: The psychological status is with data for mental retardation in light - IQ = 67, with no dynamics in terms of cognitive status.

Persistence of seizures and results of investigated serum levels of anticonvulsants implies correction of antiepileptic therapy with an increase in the daily dose of Lamictal to 250 mg, with no change in the dose of Depakin Chrono - 900 mg/day, with reduction of seizures.

DISCUSSION

The described clinical case is a patient with congenital FHH, at the onset of the disease with hypoglycaemic-

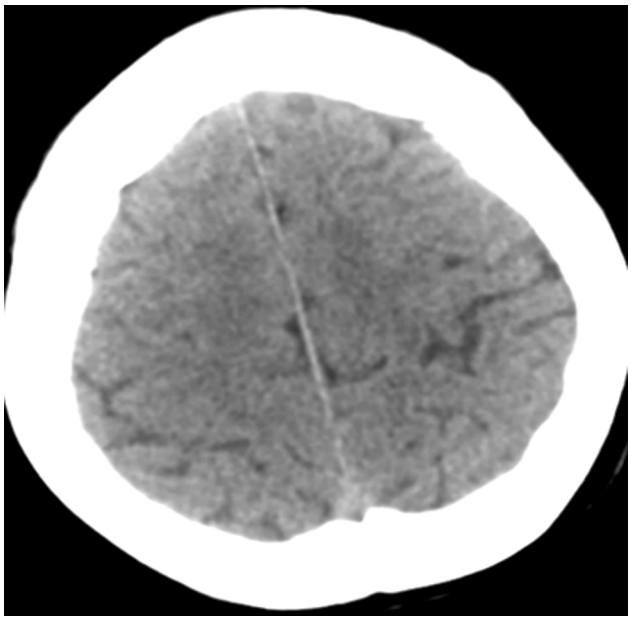

Figure 2. CT of the cerebrum with non-compliant for the age cerebral cortical atrophy mainly in temporal and parietal lobs.

induced epileptic seizures, subsequently and at normal blood sugar levels, as a result of metabolically induced cerebral cortical atrophic changes. Our case of a patient with mental retardation and symptomatic epilepsy confirms the results of the conducted study by Menni F et al. to assess the neurological consequences in newborns and infants with PHHI.[1] The neurological development of 90 patients with PHHI was followed retrospectively in the study. Sixty-three patients were treated surgically (pancreatectomy) and 27 received conservative treatment. Fifty-four patients were newborns, and of these conservative treatment was administered to 8, while 46 were operated (19 for focal adenomatous hyperplasia of the pancreas and 27 for diffuse HI). The reported results showed the following: severe psychomotor retardation in 7 patients, 6 of whom with neonatal onset of PHHI; moderate degree of psychomotor impairment in 12 patients; in 16 of them, epilepsy was established. According to the authors, the neonatal onset of hypoglycaemia is the main risk factor for severe mental retardation and/or epilepsy.[1] Patients with conservative treatment were less affected than those treated by surgical intervention and no difference was established between patients with diffuse and focal forms of HH. According to the study of Herrera A et al., diazoxide is typically a safe, effective therapy for patients with hyperinsulinism, but careful surveillance for more common adverse effects, including neutropenia, thrombocytopenia, and hyperuricemia, is warranted. PH may be more common among premature infants, as well as patients with baseline cardiac or pulmonary disease. To decrease the risk for fluid retention, chlorothiazide or an alternative diuretic should be started with diazoxide in all patients. In patients at greater risk for pulmonary hypertension due to baseline comorbidities or birth history, alternative therapies for hyperinsulinism should be considered.[6] In our case, at the onset of the disease, direct pathogenetic and surgical treatment was not conducted due to late etiological diagnosis.

Hyperinsulinism in early childhood is responsible for the ongoing very severe hypoglycaemia, which is often 1 mmol/L. These episodes are particularly dangerous as there is no alternative fuel for the brain (no lactate and no ketone bodies).[5] Glucose is an important energy source and a precursor of macromolecular constituents necessary for the rapid growth of the brain during the neonatal period and is essential for cerebral functioning.[7,8] According to the observations of Baker L et al.[9] in practice in 100% of newborns with HH, the abnormality in neurological status is with a consequent severe retardation in neuromental development, lacking other specific events in their follow-up, which may be related to mental status, a lack of dynamics in neurocognitive evaluation of patients has been reported over the years. The authors summarize that neonatal HH is still a severe disease with an important risk for rapid development of severe mental retardation and epilepsy.[9]

CONCLUSION

HH is a major risk factor for brain damage and subsequent neurological disability, therefore the identification and timely treatment of patients with HH is essential. The development of molecular genetics, radiologic imaging techniques (such as 18FDOPA-PET), conservative treatment with diazoxide or laparoscopic pancreatic surgery, can completely alter the clinical course in children with severe congenital forms of HH.[1]

REFERENCES

1. Menni F, de Lonlay P, Sevin C, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics 2001; 107(3):476–9.
2. Paggio A, Checchetto V, Campo A. Identification of an ATP-sensitive potassium channel in mitochondria. Nature 2019; 572(7771):609–13.
3. Rahman SA, Nessa A, Hussain K. Molecular mechanisms of congenital hyperinsulinism. J Mol Endocrinol 2015; 54(2):119–29.
4. Evans M, Amile SA. Carbohydrates as cerebral metabolic fuel. J Pediatr Endocrinol Metab 1998; 11:99–102.
5. Nessa A, Rahman SA, Hussain K. Hyperinsulinemic hypoglycemia – the molecular mechanisms. Frontiers in Endocrinology 2016; 7(2):29.
6. Herrera A, Ellen V, Givler S, et al. Prevalence of adverse events in children with congenital hyperinsulinism treated with diazoxide. J Clin Endocrinol Metab 2018; 103(12):4365–72.
7. Koh THHG, Ansley-Green A, Tarbit M, et al. Neural dysfunction during hypoglycaemia. Arch Dis Child 1998; 63:1353–58.
8. Lucas A, Morley TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. Br Med J 1988; 297:1304–08.
9. Baker L, Thornton PS, Stanley CA. Management of hyperinsulinism in infants. J Pediatr 1991; 119:755–7.

Семейная гиперинсулинемическая гипогликемия с эпилептическим синдромом, когнитивными нарушениями и обнаруженной мутацией гена ABCC 8 (SUR1): отчёт о клиническом случае

Ана Шопова, Силвия Шопова, Ирина Стефанова, Румяна Кузманова

Отделение неврологии, УМБАЛ „Св. Наум", Медицинский университет – София, София, Болгария

Адрес для корреспонденции: Ана Шопова, Отделение неврологии, УМБАЛ „Св. Наум", Медицинский университет – София, София, Болгария; E-mail: ani_veskova@abv.bg; Тел.: +359 887 338 186

Дата получения: 22 июня 2020 ♦ **Дата приемки:** 22 марта 2021 ♦ **Дата публикации:** 31 октября 2021

Образец цитирования: Shopova A, Shopova S, Stefanova I, Kuzmanova R. Familial hyperinsulinaemic hypoglycaemia with epileptic syndrome, cognitive impairment and detected mutation of the ABCC 8 (SUR1) gene: a case report. Folia Med (Plovdiv) 2021;63(5):805-8. doi: 10.3897/folmed.63.e55696.

Резюме

Гиперинсулинемическая гипогликемия (ГГ) возникает в результате нерегулируемой секреции инсулина бета-клетками поджелудочной железы. Это наиболее частая причина тяжёлой и продолжительной гипогликемии у новорожденных. ГГ является основным фактором риска повреждения мозга и последующего неврологического повреждения, поэтому выявление, быстрая диагностика и своевременное лечение пациентов с ГГ имеют решающее значение для предотвращения повреждения мозга. В данном случае предлагается краткое описание пациента с врождённым ГГ с установленной мутацией в гене ABCC8, кодирующем субъединицу SUR1 канала K-ATP. Обсуждается генеалогическое древо, клиническая картина, диагностическая оценка, неврологические последствия и их развитие в динамике с особым вниманием к эпилептическому синдрому и психическому состоянию. Достижения в области молекулярной генетики, радиографических методов, консервативного лечения или лапароскопической хирургии могут полностью изменить клинический подход к детям с тяжёлыми врождёнными формами ГГ.

Ключевые слова

врождённая гиперинсулинемическая гипогликемия, умственная отсталость, симптоматическая эпилепсия