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

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Abstract

Hyperinsulinaemic hypoglycaemia (HH) occurs as a consequence of unregulated secretion of insulin from pancreatic beta cells. It is the most common cause of severe and prolonged hypoglycaemia 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) are spontaneously active. The increase in Ca²⁺ leads to continuous release of insulin. Sulphonylurea
proven causes of HH.4,5 pancreatic hypoglycaemia and postbariatric surgery are insulinoma in adults, the syndrome of non-insulinoma with the HH in the neonatal period. In older children and number of developmental syndromes are also associated retardation, diabetes mellitus in the mother, and a large sive and dominant mutations in ABCC8/KCNJ11 and HNF1A, SLC16A1, UCP2 different genes (ABCC8, KCNJ11, GLUD1, GCK, HNF4A, 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 an 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).

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-
Hypoglycemia with Epilepsy and Retardation

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

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.

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

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Резюме

Гиперинсулинемическая гипогликемия (ГГ) возникает в результате нерегулируемой секреции инсулина бета-клетками поджелудочной железы. Это наиболее частая причина тяжёлой и продолжительной гипогликемии у новорождённых. 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 врождённой 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