Синдром аутоиммунитета к инсулину — редкая причина развития гипогликемического синдрома. Клинический случай синдрома в педиатрической практике

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Синдром аутоиммунитета к инсулину (САИ) характеризуется спонтанными гипогликемиями, сопровождающимися повышенным уровнем инсулина, наличием аутоантител к инсулину при отсутствии предшествующего использования экзогенного инсулина. Это третья по частоте причина развития гипогликемий в странах Восточной Азии. Заболевание развивается у генетически предрасположенных лиц в большинстве случаев после приема лекарств, содержащих сульфгидрильную группу (метимазол, пенициллин G и др.). Синдром характерен для взрослых и крайне редко встречается у детей. Представлен клинический случай развития САИ у 3,5-летней девочки европеоидной расы, возможной причиной которого послужил предшествующий курс лечения пиритинолом.

Ключевые слова: гипогликемия, синдром аутоиммунитета к инсулину, болезнь Хирата, аутоантитела к инсулину, лекарства, содержащие сульфгидрильную группу.

Insulin autoimmune syndrome: a rare cause of hypoglycemia. The case report of the syndrome in pediatric practice

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Insulin autoimmune syndrome (IAS) is characterized by spontaneous hypoglycemia accompanied by an increased insulin level and presence of insulin autoantibodies while no exogenous insulin was used. This disorder is the third leading cause of hypoglycemia in Southeastern Asia. The disorder develops in individuals with a genetic predisposition, mostly after they had administered drugs containing a sulfhydryl moiety, such as methimazole, penicillin g, etc. The syndrome is typical of adults and extremely rare among children. We report the case of developing IAS in a 3.5-year-old Caucasian girl, possibly induced by pyritinol therapy.

Keywords: hypoglycemia, insulin autoimmune syndrome, Hirata disease, insulin autoantibodies, drugs containing a sulfhydryl moiety.

Insulin autoimmune syndrome (IAS), also known as Hirata disease, was first reported in 1970 [1]. Characteristic clinical features of this syndrome include spontaneous hypoglycemia accompanied by elevated insulin levels and presence of insulin autoantibodies in patients, who did not previously receive exogenous insulin [1, 2]. Currently, more than 300 cases of the disease have been described in Japan alone; the highest number of cases was described among East Asian populations. The disease is 10—30 times more rare in Europe and America. In the East Asia, it is the third most common cause of hypoglycemia after iatrogenic hypoglycemia and insulinoma [1, 3]. The disease typically occurs in individuals aged 60—69 years and it is slightly more common in females [3]. Laboratory tests during episodes of hypoglycemia show very high values of immunoreactive insulin (IRI) level [3] along with significant, but less pronounced increase in C-peptide level (known as discordant IRI and C-peptide values). These changes in IRI and C-peptide values suggest the presence of insulin autoantibodies, which are determined as IRI [5, 6] during radioimmunoassay. The patients with Hirata disease who were not previously treated with insulin have high titers of insulin antibodies.

In most cases, onset of the disease is preceded by administration of medications 2—6 weeks before the disease; in 90% of cases, these are pharmaceuticals bearing SH-group: methimazole (methimazole), glutathione, captopril, α-lipoic acid (thioctacid), imipenem, penicillin G [1—4]. More rarely, the disease manifests after administration of medications, lacking sulfhydryl group: corticosteroids, α-interferon, diltiazem, tolbutamide, sodium loxoprofen [7]. The cases, where the syndrome developed without previous therapy, have been also reported.

The relationship between formation of insulin autoantibodies and drugs bearing a sulfhydryl group is attributed to the fact that SH-bearing pharmaceuticals facilitate dissociation of disulfide bridges in the insulin molecule, opening the alpha-chain to antigen-presenting cells, which results in stimulation of T cells in patients with predisposing haplotypes (especially DRB1*0406 haplotype) [2, 8].

The following mechanism of development of hypoglycemia was suggested in IAS patients. Food intake is followed by insulin secretion by the pancreas, which is mostly bound by antibodies; this manifests in the form of typical postprandial hyperglycemia, which leads to insu-

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lin hypersecretion. After a while, insulin dissociates from the complex with autoantibodies, which causes significant increase in the plasma level of active insulin and development of hypoglycemia [2, 7].

Hirata's disease often occurs in combination with other autoimmune diseases, such as Graves' disease, rheumatoid arthritis, and systemic lupus erythematosus [4]. It is believed that the IAS with underlying Graves' disease is caused by intake of anti-thyroid drugs (methimazole). This drug is the most common causative agent of IAS [1], and therefore it is important to keep in mind the risk of IAS in patients with Graves' disease, who are treated with methimazole (thiamazolum). In these patients, hypoglycemias are often oligosymptomatic and present with tremor, which is characteristic of Graves' disease even in patients with normoglycemia.

Since the early 2000s, more than 20 cases of IAS have been reported in individuals administered with α-lipoic acid (thioctacid) [7]. This medication is often included in food additives, and it is often used to treat diabetic polyneuropathy. In patients with diabetes mellitus (DM), hypoglycemia is usually considered iatrogenic, and therefore antihyperglycemic therapy is adjusted or even cancelled. Allowance for the fact that administration of thioctacid is the possible cause of IAS enables avoiding unreasonable examinations and improper treatment.

Hirata disease is characterized by genetic predisposition to the development of the syndrome. Thus, in the East Asia, HLA-DR4 are predisposing haplotypes (they occur in 97—100% of patients in Japan [9]), and DRB1*0406 is the most common haplotype (43% of patients in Japan) [2]. Other predisposing haplotypes include DQA1*0301, DQB1*0302, DRB1*0403, DRB1*0407 [4, 10].

IAS is usually characterized by favorable outcome: spontaneous remission of the disease within 1—3 months after manifestation occurs approximately in 80% of cases [10]; more rarely, recovery occurs during treatment (about 20% of cases). Withdrawal of the drug that triggered the syndrome is the most important treatment measure. These patients need a diet with frequent small meals, consumption of complex carbohydrates and restriction of easily digestible ones. In the cases, when hypoglycemia persists despite these measures, pharmacotherapy is used, which most often include glucocorticoids, more rarely — immunosuppressants (azathioprine, 6-mercaptopurine) [6]. Glucocorticoids are used in order to suppress production of autoantibodies. Plasmapheresis is another highly effective method of treatment of IAS [11].

The insulin autoimmune syndrome is extremely rare in children throughout the world. Only about 10 cases have been reported so far [4].

Case report

A 3.5-year-old girl was hospitalized to the Endocrinology Research Center complaining of recurrent hypoglycemias, which first appeared 3 weeks before admission. The patient had two episodes of seizures with underlying hypoglycemia, the minimum recorded glycemia was 1.3 mmol/l.

The patients had no episodes of hypoglycemia, symptoms of unmotivated weakness, lethargy, loss of consciousness, or seizures until the age of 3.5 years. One month before the manifestation of hypoglycemia, the patient had SARS accompanied by elevated body temperature up to 38°C for 2—3 days and received Kagocel. Previously, the child receives 2 month-long courses of Encephabol (pyritinol) and Anaferon for a few months (prevention of SARS).

At the age of 3 years 5 months, the girl suddenly developed abdominal pain in the fasted state. Seizures caused by hypoglycemia of 1.3 mmol/l developed in the ambulance. In the first three days, the patient received infusion of glucose solutions in order to stop seizures and recurrent hypoglycemia. The patient's state was stabilized under conditions of frequent small meals and watering with sweet liquid. However, daily fasting hypoglycemias persisted (1.3—2.2 mmol/l).

Hormonal examination at the place of residence with underlying hypoglycemia of 2.2 mmol/l showed high levels of insulin (17.4 μIU/ml) and C-peptide (8 ng/ml); there was no ketonuria. Doctors at the place of residence suspected organic nature of hyperinsulinism. The child was sent to Moscow for further examination.

During examination at the Endocrinology Research Center, IGF-1, GH, cortisol, and thyroid hormone levels are within the normal range **(Table 1)**. Fastentest was conducted to find out the genesis of hypoglycemia. Three-hour fasting period resulted in development of hypoglycemia (2.5 mmol/l) and abnormally high level of insulin (> 1000 μU/ml), high levels of C-peptide (16 ng/ml), and low blood level of ketones (0.1 mmol/l) **(Table 2)**. Given inadequately high insulin levels, repeated fastentest was carried out, which produced identical results: insulin level again exceeded 1000 μU/mL, C-peptide level — 9 ng/ml **(Table 3)**. Repeated measurement of insulin level with underlying normoglycemia showed persistent extremely high values (>1000 μU/ml). Frequent small meals were recommended and glycemic control was carried out during the day. There were no episodes of hypoglycemia, when the patient received frequent small meals and additional fast carbohydrates. However, increase in fasting period to 4 hours resulted in recurrence of hypoglycemia, but it was oligosymptomatic and easily stopped by food intake. Glycemic control during the day showed that glycemia fluctuations ranged from 2.0 to 16 mmol/l 1—1.5 hours after intake of fast carbohydrates. Oral glucose tolerance test showed abnormal increase in glycemia up to 14.7 mmol/l on the 90th minute, however glycemia was normalized within 120 minutes (6.9 mmol/l) **(Fig. 1)**.

Ultrasound examination of the abdominal cavity detected no evidence of space-occupying mass.

***Table 1*. The results of hormonal examination of the patient at admission**

Value	Result	Limits
STH	1.39 ng/ml	
IGF-1	118.5 ng/ml	8—290 ng/ml
TSH	1.8 mIU/l	0.64—5.76 mIU/l
T_4 free	16.3 pmol/l	11.5—20.4 pmol/l
Hydrocortisone	372 nmol/l	77—630 nmol/l

***Table 2*. The results of fastentest at admission**

Value	Result	Limits
Glycemia	2.5 mmol/l	> 3 mmol/l
IRI	> 1000 μU/ml	< 2 μU/mL
C-peptide	16 ng/ml	
Ketonemia	0.1 mmol/l	

***Table 3*. The results of repeated fastentest**

Value	Result	Limits
Glycemia	2.3 mmol/l	> 3 mmol/l
IRI	> 1000 μU/ml	< 2 μU/mL
C-peptide	9 ng/ml	

Thus, patient's examination and follow-up produced very contradictory results. On the one hand, atypical clinical presentation in the form of a late manifestation of the disease (only at the age of 3.5 years) and normal development of a child excludes congenital forms of hyperinsulinism. On the other hand, repeated abnormally high levels of insulin associated with both hypoglycemia and normoglycemia do not fit the picture of insulinoma. Taking into account high levels of C-peptide, iatrogenic hypoglycemia (insulin injections) was excluded. In this regard, we suspected that the girl has insulin autoimmune syndrome.

Assessment of the level of insulin autoantibodies showed that their titer is significantly increased: more than 100 U/ml (compared to the normal value of up to 10 U/ml). The level of other autoantibodies (to tyrosine phosphatase, glutamate dehydrogenase, islet cells) did not exceed the normal values **(Table 4)**. HLA-typing showed that the patient had two haplotypes, predisposing to IAS: DRB 1 04- and DQA 1 *0301.

Therefore, clinical (hyperinsulinemic hypoglycemia that occurred spontaneously in completely healthy 3.5-year-old child) and laboratory signs (extremely high insulin levels and not as a significant increase in C-peptide level, increased titers of insulin autoantibodies), as well as detection of predisposing haplotypes suggested the diagnosis of insulin autoimmune syndrome in the child.

In connection with established diagnosis and recurrent hypoglycemia even with frequent meals (3—4 hours), the patient received treatment with prednisolone at a starting dose of 20 mg/day (1.4 mg/kg/day) to suppress the immune response. A few days later, normalization of glycemia values was observed under normal feeding conditions; no episodes of hypoglycemia were detected. During repeated oral glucose tolerance test on day 11 of therapy, normoglycemia was maintained during the entire test, however IRI values (>1000 μU/ml) and insulin antibodies level (>100 U/l) were still high. The control 13.5 hour-long fastentest resulted in development of hypoglycemia (2.2 mmol/l) along with low level of ketones (0.1 mmol/l). Gradual decrease in prednisolone doses was started one week after initiation of therapy followed its complete withdrawal in 1 month.

Examination at the place of residence 2 months after the treatment showed maintained normoglycemia under normal diet conditions. Fasting glucose level was 3.5—5 mmol/l, insulin level was 29 μU/ml with glycemia of 4.6 mmol/l; 14-hour-long fastentest was negative, but there was still high level of insulin antibodies (24.4 U/ml). Eight months after completion of therapy, there was clinical normoglycemia, 13-hour-long fastentest was negative; insulin level was 4.3 μU/ppm with glycemia of 3.7 mmol/l, insulin antibody level normalized to (4.5 U/ml) **(Fig. 2)**.

In summary, normalization of patient's carbohydrate metabolism was observed since the initiation of glucocorticoid therapy, laboratory tests showed decrease in insulin antibodies 2 months after completion of therapy; complete clinical and laboratory remission of the disease was observed in 8 months.

Discussion

This case is the first description of the insulin autoimmune syndrome in a pediatric patient in the Russian Federation. It was quite difficult to determine the provoking factor in this case. Previous therapy with encephabol (pyritinol, whose structure includes a disulfide bridge, Figure 3) 1 month before the onset of the disease possibly contributed. The role of Anaferon (preparation of gamma interferon antibodies) also cannot be excluded. However, we found no previously reported cases of this syndrome related to therapy with these drugs in the literature. This case reflects the typical course of the disease: sudden onset of hypoglycemia, extremely high insulin level along with less significant increase in C-peptide level, high levels of autoantibodies to insulin, detection of specific haplotypes, normalization of glycemia resulting from immunosuppressive therapy with glucocorticoids and stable normoglycemia after its termination, tendency to decrease in insulin and insulin antibodies level 3—4 months after the onset of the disease, full normalization of laboratory values within 10 months after the onset of the disease.

Interestingly, insulin levels determined at the place of residence and at the Endocrinology Research Center

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***Table 4*. The results of autoantibody tests**

Type of antibodies	Result	Norm
Insulin antibodies (IAA)	+100 U/ml	0—10
Antibodies to glutamate dehydrogenase (GAD)	0.79 U/ml	0—1
Antibodies to tyrosine phosphatase (IA2)	<8 U/ml	0—10
Antibodies to islet cells (ICA)	0.46 U/l	0—1

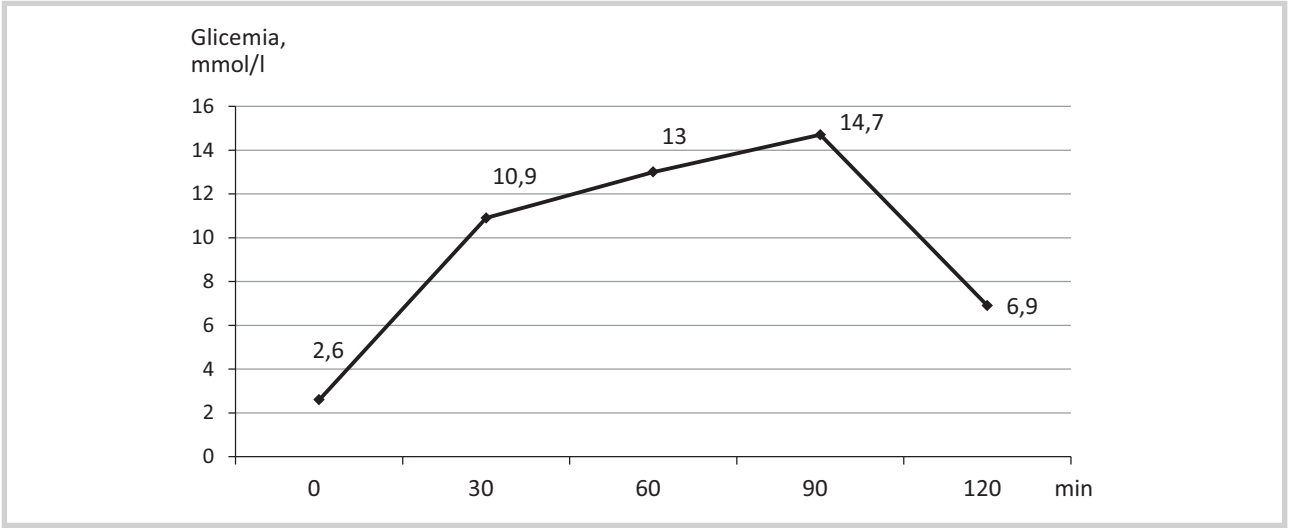

***Fig. 1*. The results of oral glucose tolerance test.**

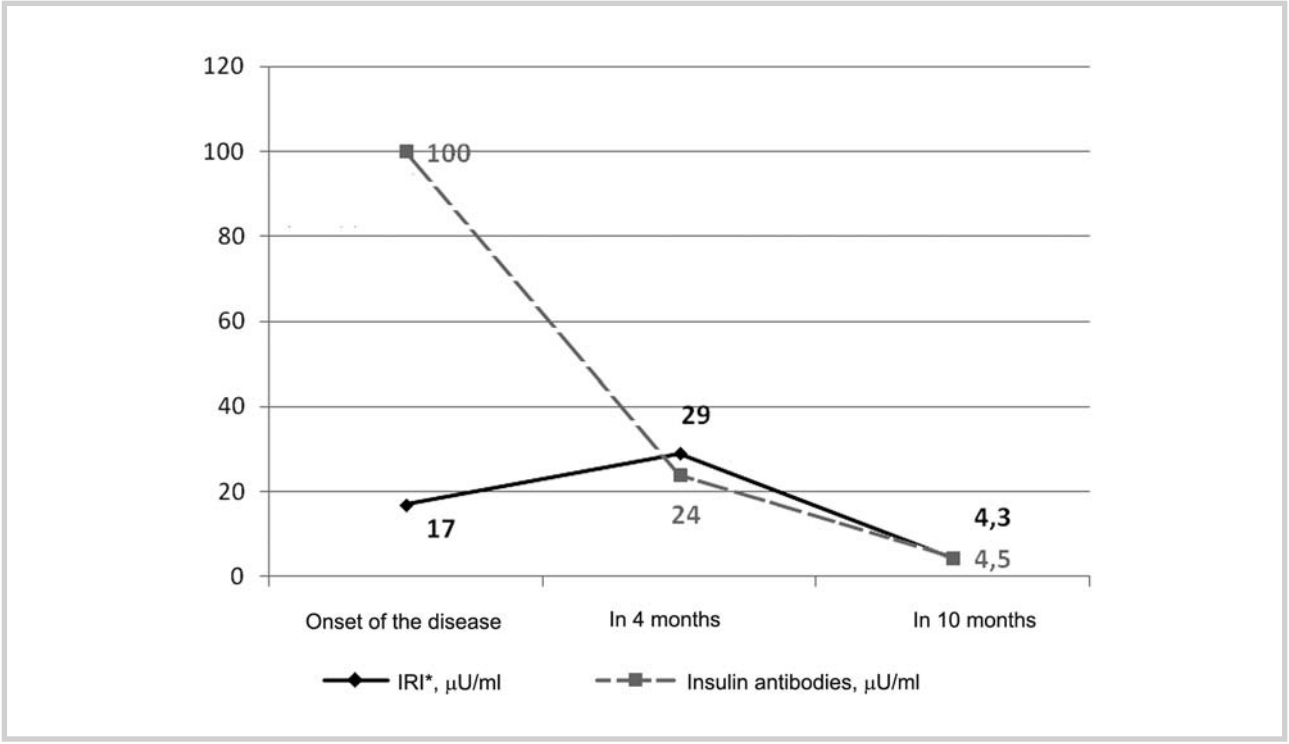

***Fig. 2*. Patient's follow-up laboratory values over time.**

Note: * — provided insulin values were determined in the laboratory at the place of residence.

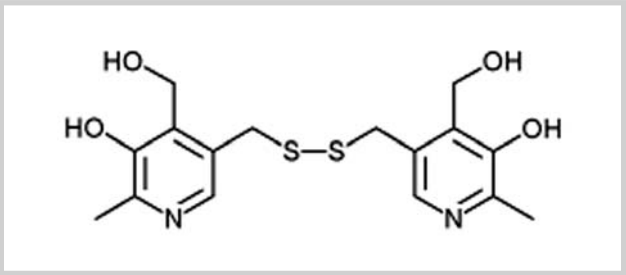

***Fig. 3*. Molecular structure of pyritinol.**

were significantly different (17 μU/ml vs >1000 μU/ml), which can be explained by different methods of insulin measurement.

The prognosis of the disease is favorable to the patient. In the future, prevention of disease relapses by elimination of provoking factors is important (in particular, exclusion of pharmaceuticals bearing SH-group).

Conclusion

This case shows that atypical clinical presentation along with extremely high insulin level and secretion of insulin autoantibodies without previous insulin therapy required inclusion of IAS to the differential diagnosis of hypoglycemic syndrome (after exclusion of iatrogenic hypoglycemia and organic hyperinsulinism). This statement is relevant for both adults and children. Diagnosis of IAS enables timely initiation of appropriate therapy (or determines expectant management, since spontaneous remission of the disease occurs in 80% of cases), and avoiding unnecessary examinations and surgery.

ADDITIONAL INFORMATION

Patient's consent. The patient voluntarily signed an informed consent for publication of the personal medical information in anonymized form in the Problems of Endocrinology journal.

Conflict of interest. The authors declare that there are neither explicit nor potential conflicts of interest associated with publication of this article.

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