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A 8-year-old boy with Down syndrome who has had a history of transient hyperinsulinemia and was found to have type 1 diabetes during ALL treatment

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Introduction

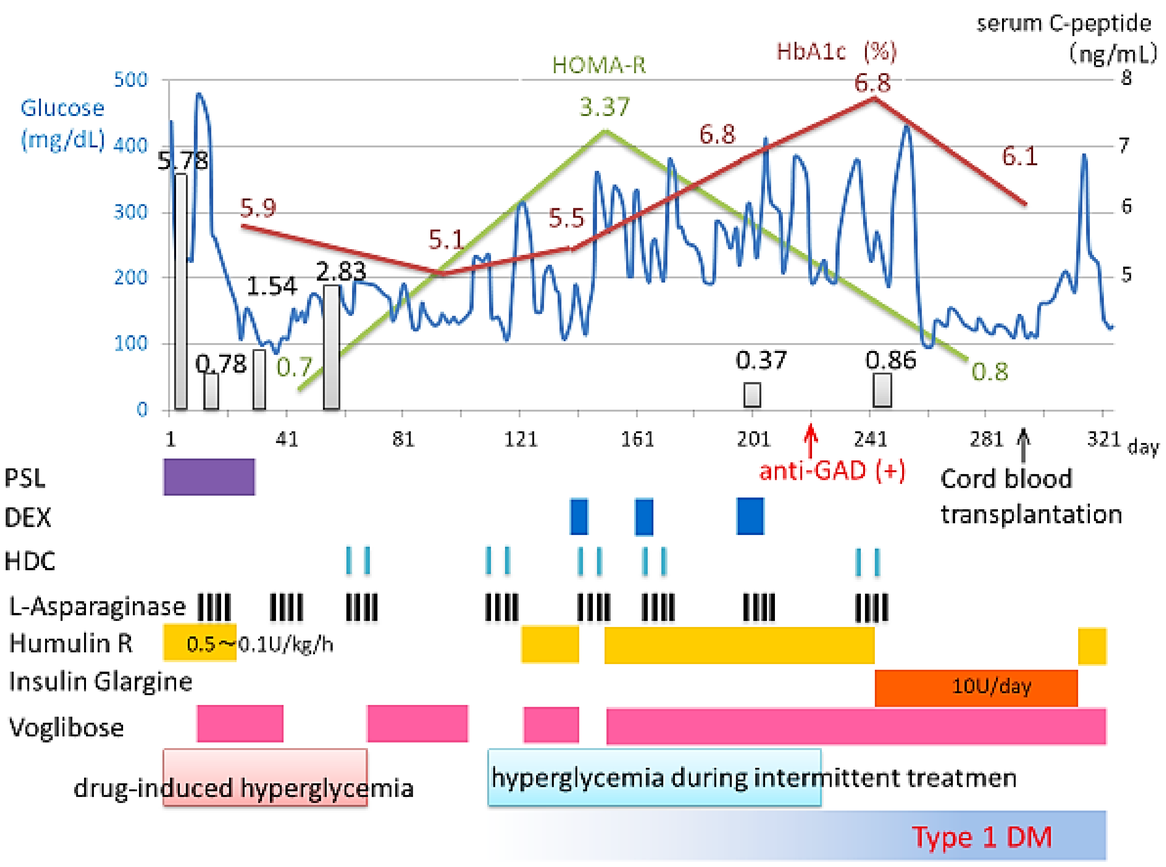
Cause of hyperglycemia in childhood has reported diabetes (type 1 & 2), drug-induced, infection, syndrome, and endocrine disease.

Case: 8-year-old boy with Down syndrome

<CC> Hyperglycemia
<PMH> # Hyperinsulinemia
Congenital hypothyroidism(Levothyroxine)
<HPI>
at birth 36week of gestation, Apgar score 7/8 (1/5min), weight 1,668g(-2.0SD), height 43.0cm(-1.3SD) ; SGA
day4 serum; glucose 41 mg/dL, insulin level 21.7 μU/mL
day11 Started taking diazoxide
day61 Finished taking diazoxide
day69 Discharge
He was not detected transient abnormal myelopoiesis at neonatal period.

8-year-old
diagnosed with precursor B-cell acute lymphoblastic leukemia
day 3 of ALL treatment with steroid, detected hyperglycemia

<PE>
height 122.4 cm (-1.0SD), weight 26.5 kg (BMI 17.6)
no pigmentation, no puberty



He started chemotherapy with a steroid, and blood sugar more than 200 mg/dl has become prolonged. Based on the combined the drug use (steroids, L-Asparaginase) and serum C-peptide immunoreactivity 5.8 ng/ml (HOMA-R 6.9) in blood, we were diagnosed with drug-induced diabetes and started insulin treatment. After that, hyperglycemia appeared only when steroids and L-Asparaginase were administered, and insulin infusion were used intermittently. Eight months after the initiation of chemotherapy, prolonged hyperglycemia and low serum C-peptide immunoreactivity levels were observed even in the intermittent period of treatment, and an anti-gultamic acid decarboxylase (anti-GAD) positive was found (12.5 U/ml), and we diagnosed type 1 diabetes. HbA1c have been difficult to evaluate accurately due to the effects of anemia and blood transfusion associated with chemotherapy.
His HLA type was DRB1*0405-DQB1*0401.

Discussion

① Classification of diabetes mellitus and glucose metabolism disorders [1)]

I.Type1 Destruction of pancreatic β cells, usually leading to absolute insulin deficiency
A. Autoimmune
B. Idiopathic

II.Type2 Ranging from predominantly insulin secretory defect, to predominantly insulin resistance with varying degrees of insulin secretory defect

III. Due to other specific mechanisms or diseases
A. Those in which specific mutations have been identified as a cause of genetic susceptibility
①Genetic abnormalities of pancreatic β-cell function
②Genetic abnormalities of insulin action
B. Those associated with other diseases or conditions
① Diseases of exocrine pancreas
② Endocrine disease
③ Liver disease
④ Drug or Chemical-induced
⑤ Infection
⑥ Rare Forms of immune-mediated diabetes
⑦ Various genetic syndromes often associated with diabetes

IV. Gestational diabetes mellitus

② High-risk HLA type of Japanese T1DM children [2)]

	Hig-risk HLA type
DR-DQ	DRB1 *0405-DQB1 *0401
	DRB1 *0802-DQB1 *0302
	DRB1 *0901-DQB1 *0303

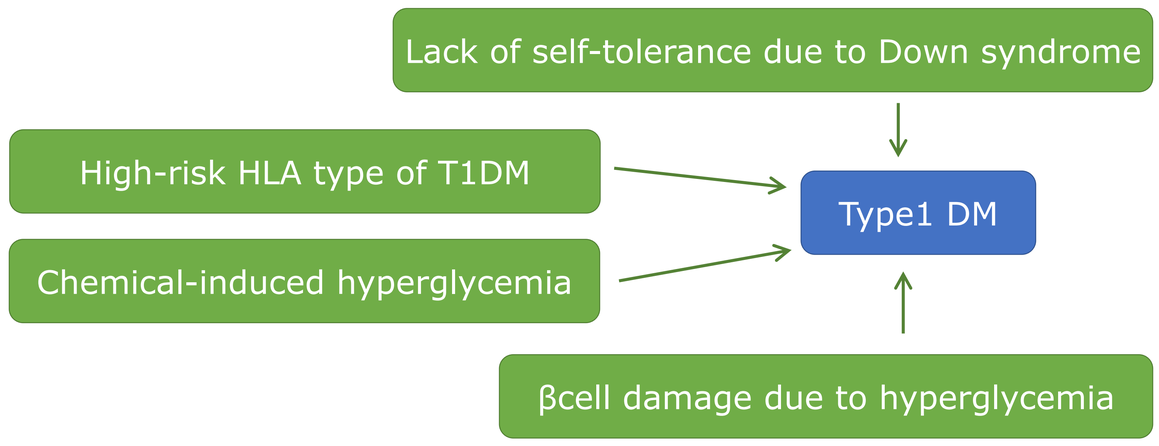
③ Lack of self-tolerance due to Down syndrome [3)]

Several studies about Down's syndrome have demonstrated alterations of both cellular and humoral immunological response mainly, secondary to alterations of the expression of autoimmune regulator gene (located on chromosome 21), leading to thymic structural and functional impairments.
It's considered that this impairments leads autoimmune thyroid disorders (i.e. Hashimoto's thyroiditis and Graves' disease) and type 1 diabetes mellitus.

④Table 3. Drugs associated with hyperglycemia[4)]

Category	Drug	Mechanism
Corticosteroids	Glucocorticoid	Increased insulin resistance
Cancer therapy	L-Asparaginase Tacrolims Cyclosporine	Reduced insulin synthesis & secretion
Protease Inhibitors	Atazanavir	Increased insulin resistance
β-blockers	Propranolol	Reduced insulin sensitivity

Because anti-GAD have not been evaluated before chemotherapy for ALL, it is unknown from when anti-GAD was presented.
In this case, it is considered that the decrease in β-cell function is due to the combined influence of THI, glucose toxicity due to drug-induced hyperglycemia, and genetic background



Conclusion

We experienced a case that presented with THI at birth was diagnosed with type 1 diabetes during ALL treatment at childhood.
Even if it is considered secondary diabetes from the treatment history, autoantibodies should measure to distinguish type 1 diabetes.

References: 1) *JDS; Classification and Diagnostic Criteria of Diabetes Mellitus. Diabetol Int 2010*, 2) *Sugihara S, et al. Diabetes 1997*, 3) *Guaraldi F,et al. Front Horm Res.2017*.
4) *2018 Up To Date; Drugs that can impair glucose tolerance or couse overt diabetes mellitus*