［Case Report］

A Pediatric Case of Graves' Hyperthyroidism with Associated Glucose Intolerance Detected by a Urine Glucose Screening Program at School

Tomomi Ikegami[1], Yukiyo Yamamoto[1,2*], Motohide Goto[1], Rinko Kawagoe[3], Yasusada Kawada[4] and Koichi Kusuhara[1]

[1] Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan

[2] Director of Medical Education, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan

[3] Department of Pediatrics, Tobata General Hospital. Tobata-ku, Kitakyushu 804-0025, Japan

[4] Department of Pediatrics, Kyushu Rosai Hospital. Kokuraminami-ku, Kitakyushu 800-0296, Japan

Abstract : We report here a 13-year-old female with Graves' disease, whose diagnostic clue was glycosuria, which was detected by a urine glucose screening program at school. She had had mild general malaise, and a physical examination revealed a slightly enlarged thyroid gland. Hyperthyroidism (thyroid-stimulating hormone (TSH) < 0.01 μU/m*l*, free triiodothyronine (fT3) 23.57 pg/m*l*, free thyroxine (fT4) 3.38 ng/d*l*) and anti-thyroid autoantibodies (TRAb 43.6%) were detected in laboratory tests, and her plasma glucose at 120 minutes was 142 mg/d*l* in a 75 g oral glucose tolerance test. She was diagnosed as having borderline diabetes. These findings revealed a diagnosis of Graves' hyperthyroidism with associated impaired glucose tolerance. Although it is reported that many adults with hyperthyroidism develop disorders of glucose metabolism, pediatric patients rarely have complications of glucose intolerance or diabetes mellitus, and there are no previous reports of Graves' disease diagnosed by a urine glucose screening program at school. This case suggests a possibility of abnormalities in glucose metabolism even in pediatric cases of Graves' disease. To avoid overlooking the diagnosis of glucose intolerance associated with hyperthyroidism, a careful medical interview and examination should be performed even if the clinical features are mild.

Keywords : Graves' disease, hyperthyroidism, glycosuria, urine glucose screening program, glucose intolerance.

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Introduction

Hyperthyroidism is characterized by an excess of thyroid hormone secretion from the thyroid gland. In both adult and pediatric patients, the most common cause of hyperthyroidism is Graves' disease, which is caused by autoantibodies that stimulate thyroid follicular cells by binding to the thyroid-stimulating hormone (TSH) receptor [1]. Excess thyroid hormone secretion stimulates gluconeogenesis and glycogenolysis, reduced insulin sensitivity, increased glucose absorption, and lipolysis, leading to deterioration of metabolic control [2−4]. Although impaired glucose tolerance has been well reported in adult patients with Graves' hyperthyroidism [5], there is little information about pediatric patients displaying glucose intolerance or diabetes.

*Corresponding Author: Yukiyo Yamamoto, MD, PhD, Director of Medical Education, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan, Tel: +81-93-691-7254, Fax: +81-93-691-9338, E-mail: y-yuki@med.uoeh-u.ac.jp

Japanese school children are screened annually for glycosuria to identify children with glucose intolerance or diabetes, and a large number of children with glucose intolerance or type 2 diabetes (T2DM) have been detected by this screening program [6]. There are no previous reports, however, of Graves' disease diagnosed with glycosuria detected by a urine glucose screening program at school. Here we report a 13-year-old female with Graves' disease with associated glucose intolerance, whose diagnostic clue was glycosuria detected by a urine glucose screening program at school.

Case report

A 13-year-old female presented to our pediatric department for glycosuria detected by a urine glucose screening program at school. It was the first time for her to have glycosuria pointed out in this screening program. She had been unaware of symptoms of diabetes such as polydipsia or polyuria.

She had had mild general malaise and weight loss of 1 kg despite having a good appetite for several months. She did not visit a hospital, because these symptoms were mild and there were no findings suggestive of hyperthyroidism.

She had no remarkable past history, but in her family history her father had been diagnosed as having type 1 diabetes at 26 years old. Her maternal grandmother had Hashimoto's disease.

A physical examination revealed a well-developed adolescent female with height of 159.8 cm (+ 0.85 SD) and weight of 53.4 kg (% obesity 11.3%). Her blood pressure was 124/70 mmHg, and her heart rate was 96 bpm. Abnormal examination findings included a slightly enlarged thyroid gland that was symmetrical and soft to palpation. In a neurologic examination, slight finger tremor was seen. Her ophthalmic, cardiovascular, respiratory and abdominal examinations were normal.

The laboratory tests show (Table 1) the liver and renal function test results were normal, and no electrolyte abnormalities were detected. The results of the 75 g oral glucose tolerance test (OGTT) (Table 2), the fasting plasma glucose level was 86 mg/d*l* and the blood immunoreactive insulin (IRI) level was 4.1 μU/m*l*, and plasma glucose at 120 minutes was 142 mg/d*l*. She was diagnosed as having borderline diabetes.

We performed a thyroid function test because of her symptoms of hyperthyroidism and thyroid enlargement, although these clinical symptoms were very mild. As shown in Table 1, her laboratory findings revealed an undetectably low level of TSH, elevated free triiodothyronine (fT3) and free thyroxine (fT4) levels, and a high antibody level. An ultrasound examination showed a diffusely enlarged and low echoic thyroid without nodules, and increased blood flow. Based on the results of the thyroid function test and ultrasound examination, she was diagnosed as having hyperthyroidism due to Graves' disease.

Treatment with methimazole 15 mg once daily was started, however as the hyperthyroidism did not improve, the methimazole was increased to 30 mg once daily, and potassium iodide (KI) 50 mg daily was added. After that, her symptoms of hyperthyroidism gradually improved. Accordingly, glycosuria was not seen soon after treatment for Graves' disease was started.

Table 1. Laboratory findings of the patient

Blood biochemistry		Endocrinology	
AST	21 IU/*l*	HbA1c	5.3%
ALT	23 IU/*l*	Anti-GAD-antibody	< 0.3 U/m*l* (NR: < 1.4)
T-chol	111 mg/d*l*	Urine CPR	212 μg/day (NR: 40～100)
TG	36 mg/d*l*		
Na	144 mEq/*l*	TSH	< 0.01 μU/m*l* (NR: 138～145)
K	4.0 mEq/*l*	fT3	23.57 pg/m*l* (NR: 3.6～4.8)
Cl	104 mEq/*l*	fT4	3.38 ng/d*l* (NR: 99～109)
Ca	10.0 mEq/*l*	TRAb	43.6% (NR: −10～10)
iP	4.8 mEq/*l*	TSAb	2.863% (NR: < 120)

AST: aspartate aminotransferase, ALT: alanine aminotransferase, T-chol: total cholesterol, TG: triglyceride, Na: sodium, K: potassium, Cl: chloride, iP: inorganic phosphorus, HbA1c: hemoglobin A1c, GAD: glutamic acid decarboxylase, CPR: C-peptide immunoreactivity, TSH: thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, TRAb: TSH receptor antibody, TSAb: thyroid stimulating antibody, NR: Normal Range

Table 2. The results of the 75 g oral glucose tolerance test (OGTT)

Time (minutes)	0	30	60	120
plasma glucose (mg/d*l*)	86	186	240	142
IRI (IU/*l*)	4.1	35.6	43.7	38.6

IRI: immunoreactive insulin

Discussion

In this report, we presented a pediatric case of Graves' disease with associated glucose intolerance, detected by a urine glucose screening program at school. The patient showed only mild clinical features of hyperthyroidism, and glucose intolerance or diabetes is a rare complication associated with hyperthyroidism in pediatric cases. Although disorders of glucose metabolism can be seen even in the early stage of the disease, a diagnosis of impaired glucose metabolism caused by hyperthyroidism might be overlooked when we only focus on definitive clinical features.

Autoimmune thyroid disease and autoimmune diabetes are common autoimmune endocrine diseases in childhood, and their coexistence in the same patient is defined as autoimmune polyglandular syndrome (APS) [7]. Graves' disease has been reported to have a high risk of type 1 diabetes mellitus (T1DM), and patients with the former should be screened for autoantibodies associated with diabetes [8, 9]. In our case, T1DM was rejected, because both antibodies for glutamic acid decarboxylase autoantibodies and insulinoma-2-associated autoantibodies were negative, but autoantibodies should be checked for periodically in the future.

Other than autoimmune diabetes, patients with hyperthyroidism show a much higher rate of abnormal glucose metabolism than the general population [5, 10]. Although the mechanism is not fully understood, a number of mechanisms underlying glucose intolerance in hyperthyroidism have been proposed in previous studies. Both impaired insulin secretion and decreased peripheral insulin sensitivity are factors that contribute to an abnormal glucose tolerance in the hyperthyroid state [5, 11]. Patients with hyperthyroidism show marked insulin resistance to oral glucose tolerance tests [12]. Glucose uptake in the skeletal muscle is known to be lower in hyperthyroid patients than in euthyroid patients [13, 14]. Impairment in insulin secretion, along with increased metabolic clearance of insulin, have been reported in the hyperthyroid state [11, 15, 16]. An increase in intestinal absorption of carbohydrates [17], hepatic glycogenolysis, and gluconeogenesis have also been reported in hyperthyroidism [18–20]. Alterations in gastric emptying, blunted insulin receptor binding, decreased glucose utilization, and enhanced lipid oxidation and hepatic glucose production due to the influence of catecholamines and glucagon have also been demonstrated [4, 21–24].

Several reports have demonstrated that the risk for glucose intolerance increases with age. Paul *et al* reported a rate of 72.3% in 65 patients with hyperthyroidism aged 20–60 years [25], and Roubsanthisuk *et al* reported a rate of 39.4% in 38 patients with hyperthyroidism aged 16–56 years [11]. Age-related β-cell dysfunction and reduction of insulin sensitivity are usually observed [26, 27]. It seems that these factors increase the abnormal glucose metabolism in adult patients with Graves' disease. In contrast, glucose intolerance has not been a significant risk in pediatric cases. Roubsanthisuk *et al* demonstrated that glucose intolerance diagnosed by oral glucose tolerance testing was absent in patients under 21 years of age [11]. Although the risk for glucose intolerance is lower than in adults, our case report showed that hyperthyroidism could proceed to glucose intolerance in pediatric patients, indicating the importance of recognizing the presence of glucose intolerance. In a patient presenting with glycosuria and a diagnosis of impaired glucose tolerance, thyroid function should be examined, even in a case with mild glucose intolerance or mild signs of hyperthyroidism. Early diagnosis and treatment of coexisting Graves' disease in pediatric patients with glucose intolerance or diabetes can result in better thyroid and glycemic control.

Not only hyperthyroidism, but also other endocrine diseases can be associated with glucose intolerance or diabetes, and could be falsely diagnosed as T2DM. Glucose metabolism can be directly or indirectly affected by excessive hormone production [28]. Acromegaly, Cushing's syndrome and pheochromocytoma can increase glucose production and cause insulin resistance [28]. When clinical features suggest an endocrine disease, careful medical interview and examination are needed to avoid overlooking underlying diseases and unnecessary escalation of treatment for diabetes [28].

Detection of hyperthyroidism in patients with glucose intolerance or diabetes seems to have clinical implications. If hyperthyroidism is not treated in a timely manner, the continuous effects of high thyroid hormone levels can irreversibly damage β-cells, leading to incurable diabetes [29]. Glucose metabolism abnormality

is also an important risk factor for cardiovascular disease (CVD) [30−33]. It has been reported that Graves' disease patients with diabetes who were misdiagnosed as not having the disease by hemoglobin A1c (HbA1c) were at high risk for CVD, assessed by the Framingham risk score. Therefore, an early differentiation between glucose intolerance and diabetes is particularly important. An abnormal glucose tolerance in hyperthyroidism was reported to reverse to normal glucose tolerance after achieving euthyroid status [5, 34, 35]. Glucose tolerance should have been assessed after achieving a stable euthyroid state in our case.

In conclusion, our case suggests a possibility of abnormalities in glucose metabolism even in pediatric cases of Graves' disease, even in the early stage of the disease. A careful medical interview and examination should be performed, even if clinical features are mild, in order to avoid overlooking a diagnosis of glucose intolerance associated with hyperthyroidism.

Conflicts of Interest

The authors declare no conflict of interest.

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学校検尿での尿糖陽性精査で判明したバセドウ病に伴う耐糖能異常の小児例

池上　朋未[1], 山本　幸代[1,2], 後藤　元秀[1], 川越　倫子[3], 河田　泰定[4], 楠原　浩一[1]

[1] 産業医科大学　医学部　小児科学講座
[2] 産業医科大学　医学部　医学教育担当教員
[3] 戸畑総合病院　小児科
[4] 九州労災病院　小児科

要　　　旨：学校検尿での尿糖陽性を契機に, バセドウ病による甲状腺機能亢進症, およびそれに伴う耐糖能異常と診断した小児例を報告する. 症例は13歳女児. 学校検尿で尿糖陽性が判明した. 多飲や多尿の自覚はなかった. 受診時, 倦怠感, 甲状腺腫が認められ, 甲状腺機能亢進（TSH < 0.01 μU/m*l*, fT3 23.57 pg/m*l*, fT4 3.38 ng/d*l*）, 自己抗体陽性（TRAb 43.6%）で, バセドウ病と診断した. 経口ブドウ糖負荷試験（OGTT）では負荷後120分血糖のみが高値（142 mg/d*l*）で境界型であった. 成人では甲状腺機能亢進症に耐糖能異常を発症することが報告されている. 小児では耐糖能異常や糖尿病を合併した報告は稀で, 学校検尿での尿糖陽性を契機にバセドウ病が判明した例はない. 甲状腺機能亢進症に伴う耐糖能異常を見逃さないために, 臨床症状が軽微であっても慎重な問診と診察を行う必要がある.

キーワード：バセドウ病, 甲状腺機能亢進症, 糖尿病, 学校検尿, 耐糖能異常.