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A child with Down Syndrome and Type 2 Diabetic Mellitus

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ABSTRACT

Down Syndrome (DS) is one of the common chromosomal disorders that raise mental retardation. It is known that DS patients have an autoimmune disorder affecting the endocrine and non-endocrine organs. It is a rare occurrence of type 2 Diabetes Mellitus (type 2 DM) disease in children with DS. Type 2 DM occurs due to impaired insulin secretion and excessive hepatic glucose production, unlike type 1 DM, caused by the destruction of ß-cells in autoimmune Langerhans. A 10-year-old girl patient was referred from Tabanan Hospital to Sanglah Hospital, Denpasar. Patients were admitted to the hospital with decreased consciousness, treated for four days, and observed in ICU for 2 days. Vomiting twice, no seizures, urinating normally. No significant past medical history was found. Physical examinations showed a typical Mongolian face, short neck, expanded occipital area, small eyes, and a mouth with a prominent tongue. Laboratory data revealed fasting blood glucose of 473 mg/dL and an HbA1C level of 12.6%. Urinalysis showed ketone 3+. The C-peptide test showed a reasonably good ß pancreas cell function. Down syndrome is associated with autoimmune diseases, including type 1 diabetes. The exact number of down syndrome cases with type 2 DM remains unknown; however, it was known that the case is infrequent.

Keywords: Down syndrome, type 2 diabetes, autoimmune

INTRODUCTION

Down Syndrome (DS) is a genetic disorder characterized by an excess of the third chromosome in the 21st pair of chromosomes, which causes the total of chromosomes to become 47 instead of 46, as in normal individuals. It is estimated that the incidence of DS worldwide is 8 million people. According to the records of the Indonesian Center for Biodiversity and Biotechnology (ICBB) Bogor, more than 300,000 children are suffering from DS in Indonesia.[1,2] However, patients with DS with type 2 diabetes are sporadic. It has been reported in several studies that Diabetes Mellitus (DM) with DS occurs at a young age.[2,3]

Type 2 DM (formerly known as non-insulin dependent DM) is a type of diabetes characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.[4] Several studies suggest that type 2 diabetes can result from the interaction of genetic, environmental, and behavioral factors.[5,6] Down syndrome is a chromosomal disorder and the most common cause of mental retardation.

CASE REPORT

A patient, a 10-year-old girl, was referred from Tabanan Hospital to Sanglah Hospital, Denpasar. The patient was admitted to the hospital with decreased consciousness, was treated for four days, and observed in the ICU for 2 days. She vomited twice, no seizures were found, and normal defecation was reported. There was no significant past medical history, and her mother was pregnant with her at the age of 37 years. Physical examination showed apathy, blood pressure 100/60 mmHg, heart pulse 98x/minute, respiration 20x/minute with a temperature of 36.4°C. On examination of the head and neck, pale conjunctiva was found. No icterus and cyanosis, and showed typical Mongolian, short neck, widened occipital area and small eyes, small mouth with protruding tongue. Enlarged lymph nodes were not found. During a generalized status examination, no heart and lung abnormalities were found (Figure 1).

Laboratory tests performed in this study were clinical chemistry, blood gas and electrolyte analysis, urinalysis, and complete blood count. The clinical chemistry test results showed an increase in fasting blood glucose and creatinine as well as HbA1c and a decrease in potassium and Alanine Amino Transferase (ALT) levels (Table 1).

Chemical test results showed an increase in fasting blood glucose, an increase in creatinine, and HBA1c. As shown in Table 1, there was a decrease in the levels of potassium, ALT, albumin, and cholesterol. Blood gas analysis showed a reduction in pH, and a decrease in HCO3 and PCO2, which indicated a partially compensated metabolic

acidosis state (Table 2). Meanwhile, the immunoserological test showed results within normal limits (Table 3). The urinalysis showed the presence of proteinuria, glucosuria, and ketonuria (Table 4). Complete blood count revealed anemia and decreased mean corpuscular volume, mean corpuscular hemoglobin, red distribution width, and decreased thrombocytopenia, as shown in Table 5.

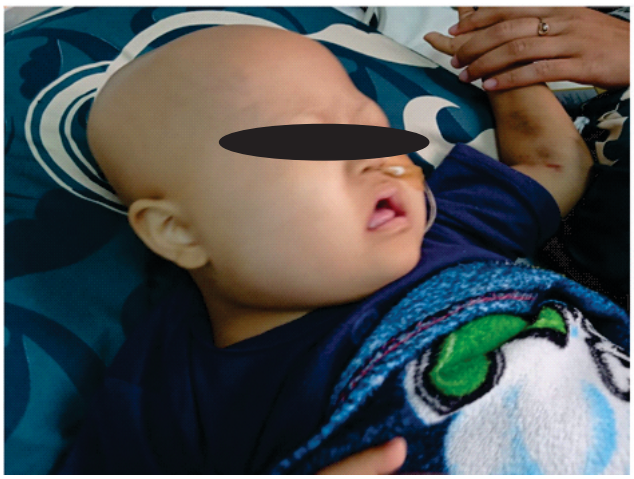

Figure 1. Mongoloid characteristic of patient's face

Table 1. Results of clinical chemistry test

Parameter	21/3/2019	22/03/2019	23/03/2019	24/3/2019	Reference Value
Fasting blood glucose (mg/dL)	473			181	60-100
BUN (mg/dL)		22.90			8.00-23.00
Creatinine (mg/dL)	1.35	1.86			0.50-0.90
Potassium (mmol/L)	1.99		2.38		3.50-5.10
Sodium (mmol/L)	135	144	143		136-145
Chloride (mmol/L)	98.1	103.8	103.0		94-110
Calcium (mg/dL)		7.0	7.6		9.20-11.00
HbA1c (%)		12.6			4.8-5.9
AST/SGOT(U/L)				13.9	11.00-27.00
ALT/SGPT(U/L)				8.70	11.00-34.00
Albumin g/dL				2.70	3.20-4.50
Total cholesterol (mg/dL)				100	140-199
Triglyceride (mg/dL)				75	< 150
HDL cholesterol (mg/dL)				47	40-65
LDL cholesterol (mg/dL)				43	< 130
Serum iron (SI)(µg/dL)		34.48			50-120
TIBC (µg/dL)		197.00			255.00-450.00
Ferritin (ng/mL)		83.42			13-68
C-peptide(ng/mL)		1.8			0.9-7.1
Fasting insulin (uIU/mL)		5.1			3.2-28.5

Table 2. Results of blood gas analysis

Parameter	21/03/2019	23/03/2019	Reference Value
pH	7.25	7.35	7.35-7.45
pCO2 (mmHg)	31.7	42.9	35.00-45.00
pO2 (mmHg)	**90.70**	83.80	80.00-100.0
BEecf (mmol/L)	-4.3	-2.5	-2-2
HCO3- (mmol/L)	20.20	22.10	22.00-26.00
SO2c (%)	99.3	95.8	95%-100%
TCO2 (mmol/L)	21.10	24.40	24.00-30.00
Sodium (mmol/L)		145	136-145
Potassium (mmol/L)		2.28	3.50-5.10
Chloride (mmol/L)		113	96-108

Table 3. Results of immunoserologic test

Parameter	21/03/2019	Reference Value
FreeT4 (ng/dL)	1.13	0.93-1.70
TSH (μIU/mL)	2.15	0.27-4.20

Table 4. Results of urinalysis

Parameter	22/03/2019	29/3/2019	31/3/2019	Reference Value
Specific gravity	1.010	1.008	1.009	1.003-1.035
Turbidity	Turbid (+)	Turbid (+)	Turbid (+)	
pH	6.50	7.00	7.00	4.5-8
Leukocytes (cells/uL)	(1+)25	(3+)500	(2+)75	Negative
Nitrite (mg/dL)	Negative	Negative	Negative	Negative
Protein (mg/dL)	(1+) 20	(1+)30	(1+)20	Negative
Glucose (mg/dL)	(2+) 200	1+)70	(1+)50	Negative
Ketone (mg/dL)	(3+) 100	Negatif		Negative
Blood (ery/uL)	(1+)	(1+)	Negative	Negative
Urobilinogen (mg/dL)	Normal	Normal	Normal	Negative
Bilirubin (mg/dL)	Negative	Negative	Negative	Negative
Color	Light yellow	Yellow	Yellow	p.yellow-yellow
Microscopic leukocytes (/FOV)	10	129	11	7
Microscopic erythrocytes (/FOV)	11	29	14	5
Epithelial cell:				
(/FOV)	5		9	
Cylinder (/FOV)	4.93	Granular+		
Crystal (/FOV)	Negative			
Etc (/FOV)	Bacteria++	Bacteria++	Bacteria+	

Table 5. Hematologic test

Parameter	21/03/2019	01/04/2019	Reference Value
% Reticulocytes	6.4		
WBC (10^3/μL)	4.42	3.27	4.1-11.0
% Neu	70.94	43.41	47-80
%Lym	14.93	28.60	13-40
%Mono	12.52	24.85	2.0-11.0
%Eos	1.08	1.54	0.0-5.0
%Baso	0.53	1.60	0.0-2.0
RBC (10^6/μL)	3.38	3.34	4.0-5.2
HGB (g/dL)	7.71	7.64	12.0-16.0
HCT (%)	25.44	26.20	36.0-46.0
MCV (fL)	75.16	78.46	80.0-100.0
MCH (pg)	22.79	22.88	26.0-34.0
MCHC (g/dL)	30.32	29.17	31-36
RDW (%)	24.81	25.75	11.6-14.8
PLT (10μ/μL)	103.90	352.50	140-440
MPV (fL)	7.56	6.25	6.80-10.0

Based on the medical history, physical examination, and further investigations, the patient was diagnosed with diabetic ketoacidosis et causa suspected with type 2 diabetes mellitus, Acute Kidney Injury (AKI) risk, with DS susp and microcytic hypochromic moderate anemia et causa susp iron deficiency anemia/chronic disease. The patient received IVFD therapy with NaCl 0.9% 18 drops per minute, drip KCL 20 mL in 500 mL maintenance fluid, Novorapid 3x10 IU before meals, and Levemir 10 IU with each meal.

DISCUSSIONS

Down syndrome is the most common autosomal chromosomal disorder in humans. The latest incidence is estimated to be 1.0-1.2 per 1000 live births. It is estimated that 20% of children with DS are born to mothers over the age of 35 years. Down syndrome can occur in all races. The most common chromosomal abnormality is trisomy. This trisomy happens when there are three main chromosomal features in addition to the regular two chromosomes. Trisomy usually results from discontinuous meiosis (failure of pairs of chromosomes to separate). Down syndrome or trisomy 21 is humans' most common mental retardation-malformation syndrome.[7] This condition used to be called mongolism because Landon Down's facial description is similar to Asian (Mongol) people. This condition is now called DS or trisomy 21. According to records from the Indonesia Center for Biodiversity and Biotechnology (ICBB), Bogor, there are more than 300 thousand children with DS in Indonesia.

Meanwhile, the incidence of DS sufferers worldwide is estimated at 8 million.[8,9] This patient has a typical mongoloid face, wide eye spacing, flat nasal bone, and macroglossia tongue. In the extremities, the hands are short and wide. A definite diagnosis of DS can be obtained from a cytogenetic examination to determine trisomy 21.[10]

Type 2 DM accounts for approximately 90% of all cases of diabetes. In type 2 diabetes, the insulin response is reduced, causing insulin resistance. In this state, the body compensates by producing insulin to maintain glucose homeostasis, resulting in hyperglycemia.[11] Type 2 diabetes is most commonly seen in children, adolescents, and younger adults due to increasing rates of obesity, lack of physical activity, and energy-rich diets. Most type 2 DM patients are obese or have a higher body fat percentage. Adipose tissue promotes insulin resistance through various inflammatory mechanisms, including increased release of Free Fatty Acid (FFA) and adipokine dysregulation.[3]

Patients with DS associated with type 2 DM are very rarely reported. Several studies have shown that type 2 DM with DS occurs at a younger age with obesity or overweight.[1] The distribution of fat, especially in the periphery, is closely related to the muscle hypotonicity characteristic of DS, which contributes significantly to insulin resistance. Obesity is linked to fat accumulation in the body, especially in the abdomen, and is more related to insulin resistance. Visceral adipocytes have higher basal lipolysis, which is closely associated with insulin resistance. As a result, increased lipolysis stimulates continuous glucose production. To maintain euglycemia, insulin secretion is increased to compensate in obese patients, reducing insulin receptor expression (downregulation), resulting in more insulin action resistance.[4]

This patient was diagnosed with type 2 diabetes, as seen from the blood glucose levels of 473 mg/dL, C-peptide levels of 1.8 ng/mL, and fasting insulin of 5.1 uIU/mL. The frequency of diabetic ketoacidosis (DKA) in children is approximately 10-70%. Diabetic ketoacidosis is biochemically characterized with a triad of hyperglycemia (473 mg/dL), venous pH < 7.3 (7.25) or serum bicarbonate concentration < 20 mmol/L and the presence of ketonemia and ketonuria. Diabetic ketoacidosis can also occur in patients with type 2 diabetes. Type 2 diabetes is a disease of inadequate insulin or increased insulin resistance. Pancreatic beta cell function in individuals can produce insulin in sufficient quantities to prevent ketogenesis but not sufficient for the body's glucose needs, thereby avoiding the buildup of ketones in the bloodstream. Diabetic ketoacidosis occurs in patients with type 2 diabetes when insulin production is insufficient (or absent) to prevent ketone production with or without precipitating factors.[5]

References suggest that DKA in patients with type 2 diabetes presents a less severe acidosis and that patients are more likely to have decreased or normal potassium levels.[8] Patients with type 2 diabetes and DKA also tend to have a higher body mass index and shorter duration of diabetes with variable age of onset. In DKA showing increased beta cell function, measuring C-peptide after glucagon administration is necessary to differentiate patients as type 1 or type 2 when DKA occurs for the first time. This test helps to identify residual beta cell function and can help predict whether the patient will require further insulin therapy in the future.[5] C-peptide levels were normal in these patients, suggesting a type 2 DM. Serum potassium was decreased as a secondary consequence of acidosis. Total body calcium stores are reduced in DKA but are not accurately reflected by their serum levels due to hypovolemia and hyperglycemia. An increase in serum creatinine level demonstrates a decrease in intravascular volume. Disruption of acetoacetate can incorrectly increase serum creatinine measurements. Decreased cholesterol is also often found.[6] Normal serum sodium in DKA indicates a deeper water deficit.[6]

In this case, the patient experienced a loss of consciousness upon admission to the hospital. From

the results of laboratory tests, blood glucose was 473 mg/dL, pH 7.25, and urinalysis indicated ketonuria. The three triads of DKA in this patient were met. The condition of the patient with decreased consciousness indicated a severe illness. Diabetic ketoacidosis is associated with a variety of acid-base, hydration, and electrolyte disturbances. Acute Kidney Injury (AKI) is one of the complications of DKA. Acute kidney injury can be inferred from laboratory tests and is related to the severity of the hyperglycemic crisis. In this case, AKI results primarily from hypovolemia due to glucose-induced osmotic polyuria and occasionally emesis.[7]

Acute kidney injury is characterized by a sudden decline in kidney function resulting in the retention of nitrogen and other waste products that are normally cleared by the kidneys. Acute kidney injury is not a single disease but rather represents a heterogeneous group of conditions that share common diagnostic features such as elevated BUN concentrations and/or increases in plasma or Serum Creatinine (SCr) and are often associated with reduced urine volume. The incidence of AKI has more than quadrupled in the United States since 1988. It is estimated to have an annual incidence of 500 per 100,000, higher than the annual incidence of stroke. Acute kidney injury is associated with an increased risk of death in hospitalized patients, particularly those admitted to the ICU, where the in-hospital mortality rate may exceed 50%. The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and post-renal obstruction. An increase in SCr concentration usually infers the presence of AKI. Acute kidney injury is currently defined as an increase from baseline of at least 0.3 mg/dL within 48 hours or at least 50% higher than baseline at one week or a decrease in urine output to less than 0.5 mL/kg per hour for more than six weeks.[8] The cause of AKI in a hyperglycemic crisis is often prerenal.[10,11] Renal hypoperfusion results from hypovolemia from osmotic polyuria and occasionally gastrointestinal loss. According to the acid-base status, AKI patients showed higher blood glucose on admission to the ICU. This result can be explained by at least two of the following causes. First, AKI appears to be associated with inflammation and insulin resistance in critically ill patients. Second, renal failure may be related to lower glycosuria, which effectively limits hyperglycemia. When blood glucose remains within the physiological level, it will be reabsorbed by the kidneys. This process coincides with sodium reabsorption and mainly involves two cotransporters, Sodium-Glucose Linked Transporters (SGLT) 1 and 2. Glucose uptake by SGLT 1 and 2 in diabetic patients is increased. However, glycosuria will limit hyperglycemia when hyperglycemia exceeds the threshold value for glucose reabsorption.[8]

In this case, the patient had AKI as seen from the results of serum creatinine, which increased by more than 0.3 mg/dL within 48 hours, from 1.35 to 1.86 mg/dL. The cause of AKI in this patient was prerenal due to hyperglycemia caused by insulin resistance in DKA. This patient's management was carried out by lowering blood glucose and acid-base balance. In addition, fluid therapy has been fulfilled, and the patient has shown clinical improvement. Hyperglycemia has a direct relationship with the development of inflammatory conditions indicated by increased expression of proinflammatory cytokines such as IL-6 and TNF-α. Studies show that a longer duration of the disease and/or the loss of glycemic control involves a higher inflammatory process. Increased proinflammatory cytokines play an essential role in insulin resistance and induce the emergence of cardiovascular and micro-macrovascular complications of diabetes, kidney disease, and anemia. By increasing mainly IL-6, an antierythropoietic effect occurs, as this cytokine alters the sensitivity of the progenitor to erythropoietin (erythroid growth factor) and also promotes apoptosis of immature erythrocytes, causing a decrease in the number of circulating erythrocytes and consequently leads to a reduction in hemoglobin. It should also be noted that the development of diabetic nephropathy further impairs the production of erythropoietin by the kidneys. Therefore, diabetics who are at risk of impaired kidney function have a high risk of developing anemia.[11]

This patient had microcytic hypochromic anemia. According to the diagnostic flow of hypochromic anemia by Samir, it is determined by evaluating the Reticulocyte Production Index (RPI). This patient had an RPI < 2, normal ferritin (83.42 ng/mL), and a decreased TIBC level (197.00 ng/dL), which was consistent with anemia due to type 2 DM as a chronic disease.

The incidence of type 2 DM in children with DS is extremely rare, and type 1 DM is more commonly found in children with DS type 1 DM. This fact is due to an autoimmune mechanism in type 1 diabetes in children with DS. However, the exact number of type 2 DM with DS remains unknown, and it is only suggested that its number is scarce.

No chromosomal test remains the limitation in this case. Making the diagnosis of DS was merely based on physical examination.

CONCLUSIONS

Further investigation into this patient was urgently needed. Cytogenic examination and glutamate acid decarboxylase antibody test can prove any coincidental relationship or genetic basis between type 2 diabetes and DS.

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