Diabetes insipidus in neuropsychiatric-systemic lupus erythematosus patient

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Systemic lupus erythematosus (SLE) is an idiopathic autoimmune chronic inflammatory disease that is unique in its diversity of clinical manifestations, variability of disease's progression, and prognosis. The disease is characterized by the remission and multiple flare-ups in between the chronic phase that may affect many organ systems.[1]

The prevalence of SLE in the US population is 1:1000 with a woman to man ratio of about 9-14:1. At Cipto Mangunkusumo Hospital, Jakarta in 2002, there was 1.4% cases of SLE of the total number of patients at the Rheumatology Clinic. Neuropsychiatric manifestations of SLE (NP-SLE) have a high mortality and morbidity rates. The incidence of NP-SLE ranges 18-61%. Diagnosis of NP-SLE is difficult because there is no specific laboratory examination. Accordingly, in all SLE patients with central nervous system (CNS) dysfunction, additional tests will be necessary to confirm an NP-SLE diagnosis and exclude other causes.[1,2]

Similar to diabetes insipidus, SLE is a systemic disease which affects many organ systems, one being the endocrine system. No data has specified the occurrence rate of diabetes insipidus in SLE patients. This disease arises from a number of factors able to interfere with the mechanism of neurohypophyseal renal reflex resulting in the body's failure to convert water.[3] There are three general forms of the disease, a polydipsic-polyuric syndrome caused by partial/complete vasopressin deficiency (central-diabetes-insipidus/CDI), vasopressin resistance of the kidney tubules (nephrogenic-diabetes-insipidus/NDI), and primary polydipsia. CDI occurs in about 1 in 25,000 persons.[4]

CASE ILLUSTRATION

A woman, 25 years old, was admitted to hospital with main complaint being a decline in consciousness one day before hospitalization. For 3 months she has complained of joint pains, hot-flushes and facial rash, especially when exposed to sunlight, the progressive hair loss and aphthae. Since a month ago, she has been diagnosed lupus and was given the prednisone 4 tablets t.i.d. Two days before hospitalization, she had convulsions for about 2 minutes. Her body was stiff. While having convulsions, she lost consciousness, but came to thereafter. Since yesterday, she has not been able to communicate with people. She had never complained of headache or fever. Her weight has decreased 7 kg in 2 months. No history of previous convulsions, trauma, or abnormality during pregnancy, labor, and childbirth were noted.

Upon physical examination, her general condition indicated severe illness, delirium. Her blood pressure was 100/70 mmHg, pulse rate was 76 times/minutes, respiratory rate was 28 times/minute, and temperature was 36°C. The nutritional status was below average (body mass index was 17.4).Discoid rash was found on the face and all over the body. The conjunctiva was pale. Aphtae on buccal mucose was found. Upon examination of the lungs, heart, and extremities no abnormality was found. Upon neurological examination: GCS 13, no sign of meningismus or other neurological abnormalities.

Upon laboratory examination, Hb 9.6 g/dL, Ht 29%, MCV 83 fl, MCH 28 fl, MCHC 34 g/dL, leukocyte 6.400/µL, platelet 272,000/µL, diff count -/-/-/84/14/2, reticulocyte 1.5%, anti-ribosomal P protein antibody (+), anti-dsDNA (-), Lupus-anticoagulant (-), Coomb's test (-). Hemostasis: PT 11" (control 12"), APTT 42" (control 38"), INR 0.93 (control 0.99), Fibrinogen 161 mg/dL (control 279 mg/dL), D-Dimer 1030 Ug/l. ACA IgG (+) (8.395, normal value < 2.418), ACA IgM (-). Upon CT-scanning, the head showed no bleeding, nor infarct/SOL. EEG was suspected to be abnormal in the form of asynchronous bilateral slowdown.

The problems established in this patient were SLE with neuropsychiatric manifestation with vasculitis and anemia. Methylprednisolone of 500 mg b.i.d (iv drip) was administered to this patient for three consecutive days, continued with 500 mg methylprednisolone once daily for two days. Continued with cyclophosphamide 500 mg every 2 weeks (total dose of 3 g) and prednisone 1 mg/kg BW/day. Other therapies given were CaCO3 500 mg b.i.d, omeprazole 20 mg, diazepam 10 mg iv (if needed), fenitoin 100 mg t.i.d, folic acid 1 mg, heparin 2 times 5000 IU SC, continued with warfarin 2 mg once daily, aspirin 1 x 80 mg.

After 13 days of the administration of cyclophosphamide, the patient began to gain conciousness. However, in the 6th day after first administration of cyclophosphamide, this patient had hemorrhagic-cystitis. In order to cope with the problem, mesna 400 mg and adequate liquid was administered to the patient.

On the 26th day of hospitalization, the patient had a hypovolemic shock as a result of polyuria. This patient's urine volume ranged between 6000-8500 cc/day with urine gravity was 1.003. It was assumed that polyuria is associated with NP-SLE. The next step was to conduct fluid deprivation test (Martin Goldberg). This test indicated no increase in the urine gravity while the patient was fasting (the urine gravity remained 1.003) (table 1).

Table 1 Water deprivation test

Hour	Blood pressure (mmHg)	Pulse rate (x/min)	Urine Volume (ml)	Urine gravity	Weight (kg)
09:00	100/60	100	(starting)	1.004	43.5
10:00	100/60	104	500	1.003	42.5
11:00	110/60	108	300	1.003	42.5
12:00	100/60	104	300	1.003	42

Serum osmolality, pre-test: 266 (N = 280-300), post-test: 274 (N = 275-295)

Management of the diabetes insipidus in this patient was the administration of Minirin® (desmopressin) spray ll puff b.i.d and ¾ of the fluid discharged (negative-balance). During observation, the urine-volume was decreased while urine-gravity was increased (table 2).

Table 2 Recapitulation of UMU

Date	6/9	7/9	8/9	9/9	12/9	13/9*	14/9	15/9	16/9	17/9	18/9	19/9	20/*9	21/9
Intravenous solution	6250	2250	6000	6000	8000	4000	500	2000	1850	1700	1750	1500	1250	0
Drink	1500	1500	2450	3150	3000	1500	2700	2000	1750	2500	2500	2500	2500	2200
Urine vol.	8400	8400	8100	10600	11600	6500	8000	4000	3950	3600	3100	2350	2850	1800
IWL	500	500	500	500	500	250	500	500	500	500	500	500	500	500
Fluid balance	-1150	-5150	-150	-1950		-1250 (12 hours)	-800	-500	-500	100	650	150	450	-100
Urine gravity			1,003		1,003		1,006	1,007	1,009	1,009	1,008	1,008		1,007

* Minirin® starts

During hospitalization, this patient also had depression with psychotic disorder with auditory hallucinations, free association, and interference of reality. Therefore, fluoxetin 20 mg once daily and trihexyphenydil 2 mg b.i.d were administered.

DISCUSSION

The diagnosis of SLE in this patient based on the American College of Rheumatology 1997 criteria, were malar rash, photosensitivity, oral ulcers, neurological dysfunction, and ANA (+) (anti-ribosomal P protein antibody (+)).[1] This was severe and life-threatening cases with seizure and reduced level of consciousness (NP-SLE). Secondary causes of CNS dysfunction such as metabolic disturbance and medicine were excluded. The presence of anti-ribosomal P antibodies supported the diagnosis of NP-SLE, especially with psychosis/major depression.[2,4,8]

Seizures of this patient might be caused by hypercoagulability state in which thrombosis (vasoocclusive) occured and related to antiphospolipid-antibodies (high ACA-IgG titer). Antiphospolipid-antibodies are prothrombotic which can contribute to the development of acute vasoocclusive-thrombosis, endothelial cell proliferation, and intimal fibrosis.[2] In addition, careful consideration was given to the presence of vasculitis cerebral able to cause vasoocclusion because of vasculitis dermal occurred in this patient. Consideration of the presence of microthrombi and vasculitis in this patient was based on the fact that the occurrence of NP-SLE is rare in SLE patients undergoing therapy. Although the brain CT-scan did not show any irregularity, micro-infarcts had not yet been eliminated. EEG of this patient was abnormal (bilateral asynchrony slowing), but this finding was not specific for NP-SLE.[2]

The patient was given 500 mg b.i.d methylprednisolone drip for three consecutive days continued with and 500 mg once daily methylprednisolone drip for two days. The treatment was continued with 500 mg cyclophospamide every 2 weeks (total doses 3 g) and prednisone 1mg/kgBW/day. The treatment of NP-SLE is empiric because there hasn't any controlled clinical-trials done for NP-SLE. Therefore, the treatment was determined on the severity of the presentation and suspected etiology as inflammations or thrombosis.[1,2,11] Despite cyclophospamide cannot pass the blood-brain-barrier, it is able to reduce antibody production. Thus, it could be administered to this patient, because basically, the disease arises from antibody. This patient was also treated with 2 times 5000 IU heparin SC, continued with 2 mg warfarin once daily, 80 mg aspirin once daily, and anti epileptic drug.

During medical treatment, the patient experienced hypovolemic shock as a result of polyuria (urine volume exceeded 2.5 liters/24 hours in 2 consecutive days).[12] To establish the polyuria causes, it was necessary to determine whether the diuresis had resulted from water or dissolved substances by measuring the urine specific gravity or osmolality. The urine specific gravity in this patient was 1.003. Accordingly, polyuria in this patient was pure water diuresis (urine specific gravity <1.005 or 200 mOsm.kgBW).[5] The next step was to determine the disease by conducting fluid deprivation test according to Martin-Goldberg (indirect test) in order to measure the response of osmolality and the rate of urine flow at the time of dehydration and administration of exogenous vasopressin.[4,5] During the test, the patient was fasting and intravenous fluid was discontinued. Vital signs, body-weight, volume and specific gravity of urine (with urinometer) were measured hourly.[5] This test was conducted only for 3 hours because the patient's body weight decreased 3-4% (from 43.5 kg down to 42 kg). This test indicated that the urine remained diluted (no increase in the urine specific gravity) while the patient was fasting.

This test showed that the patient had a defect in converting water. To establish diabetes insipidus diagnosis, the next step would be determining the type of diabetes insipidus, whether it

is CDI or NDI by means of DDAVP (1-desamino-8-d-arginine-vasopressin)- Minirin.[5] During the administration of Minirin, the urine volume decreased although the specific gravity did otherwise. We concluded that this patient had complete-CDI based on the patient's response to the administration of DDAVP.

CDI is a rare hypothalamus-pituitary disease due to the deficiency of arginine-vasopressin (AVP) synthesis from the hypothalamus or secretion from the neurohypophysis. The etiology of CDI is unknown in over one-third of cases classified as idiopathic-CDI. In one study, autoantibodies to AVP secreting cells (AVPaAb) were found in 23.3% of CDI patients, which is classifies as autoimmunity CDI. CDI is rarely reported in association with SLE. A case has been reported on the presence of AVPcAb in CDI patients with SLE. Interestingly, it was characterized by the presence of AVPcAb before the treatment and dissappearance after intravenous cyclophosphamid and steroid therapy with restoration of normal postpituitary function.[14] Other literature reported that CDI has been linked with vascular central nervous system damage, with which vascular impairment of the inferior hypophyseal artery system suggests that abnormal blood supply to the posterior pituitary gland is associated.[15]

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