A CASE OF DIABETES INSIPIDUS ACCOMPANYING THIRST DISORDER ASSOCIATED WITH HYPEROSMOLAR DIABETIC COMA

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Summary: The case of a 14-year-old female who suffered from hyperosmolar diabetic coma (HODC) after resection of craniopharyngioma and during treatment for hypopituitarism and diabetes insipidus is presented. In Aug. 1989, craniopharyngioma was diagnosed and she underwent resection surgery and radiotherapy. Since then, she had been on supplemental therapy with hydrocortisone and thyroxin and desmopressin (DDAVP). On Jan. 17, 1992, she fell into HODC upon ingesting a large amount of soft drink to supplement water due to persistent polyuria. She improved quickly when supplementary fluids and insulin were administered. She had demonstrated no abnormality in glucose tolerance prior to this manifestation. Insulin therapy was deemed unnecessary after her recovery from HODC.

Because of a disorder in the central nervous thirst mechaninm, she lacked the sense of thirst and concomitantly the thirst-mediated water intake in spite of elevated plasma osmolarity due to dehydration and hyperglycemia. This seemed to be the cause of her accelerating dehydration. The resulting insulin resistance then brought about her HODC. Thus, it is difficult to consider such a case of HODC as symptomatic of diabetes when no abnormality in glucose tolerance either before manifestation or after restoration can be found. It should rather be considered as a case of "dehydration hyperglycemia" and be treated as such.

Index Terms

hyperosmolar diabetic coma, dehydration

INTRODUCTION

HODC is a pathological state peculiar to diabetes, resulting from the disturbance of glucose and water metabolism. At present, the fatality rate remains high (1) (2) (3), so that early and proper treatment is essential at the time of diagnosis.

Most HODC cases have demonstrated diabetes before manifestation. It is said that the patients frequently fall into HODC triggered by infection or cerebrovascular disease. The following mechanism may be speculated: dehydration promotes the secretion of hormones which are antagonistic to insulin such as glucagon, cortisol and epinephrine, dehydration increases insulin resistance in the periphery (4) (5) or dehydration inhibits insulin secretion from

the islets of Langerhans'.

However, the fact that ketoacidosis does not occur concomitantly has not yet been clarified. We report a case which may provide some suggestion for clarifying the mechanism of HODC with specific attention to the relation between dehydration and HODC.

CASE REPORT : The patient was a 14-year-old female who demonstrated weakness of sight and walking difficulty in April 1988. In July 1989, craniopharyngioma was diagnosed. The tumor was about 3 cm in diameter with accompanying calcification which extended from supura sellar to third ventricle (Fig. 1). The tumor could not be extirpated completely, so radiotherapy by lineac, with a total radiation of 30 GY was applied. No cognitive or intellectual disorder resulted. However, she was almost blind, being able to sense only light. Postoperative examination of pituitary function (Table 1) revealed that she had panhypopituitarism. Subsequently, supplemental therapy of 20 mg/day of hydrocortisone and 75 μg/day of thyroxin was prescribed. In addition, an injection of gonadotropin (HMG/HCG) every 3 weeks was administered. The DDAVP dose was controlled on the basis of the urine and water intake per day, as diabetes insipidus and her thirst disorder were concomitant. Because of her thirst disorder, she did not feel thirsty even when her plasma osmolarity was as high as 320 mOsm/L. Daily water intake was calculated on the basis of urine volume and given by her mother. Her weidght was 53.9 kg with a height of 146 cm, with a normal height increase (4.0 cm/year) in spite of her growth hormone secretion disorder. She showed 15 % obesity but no abnormality in glucose

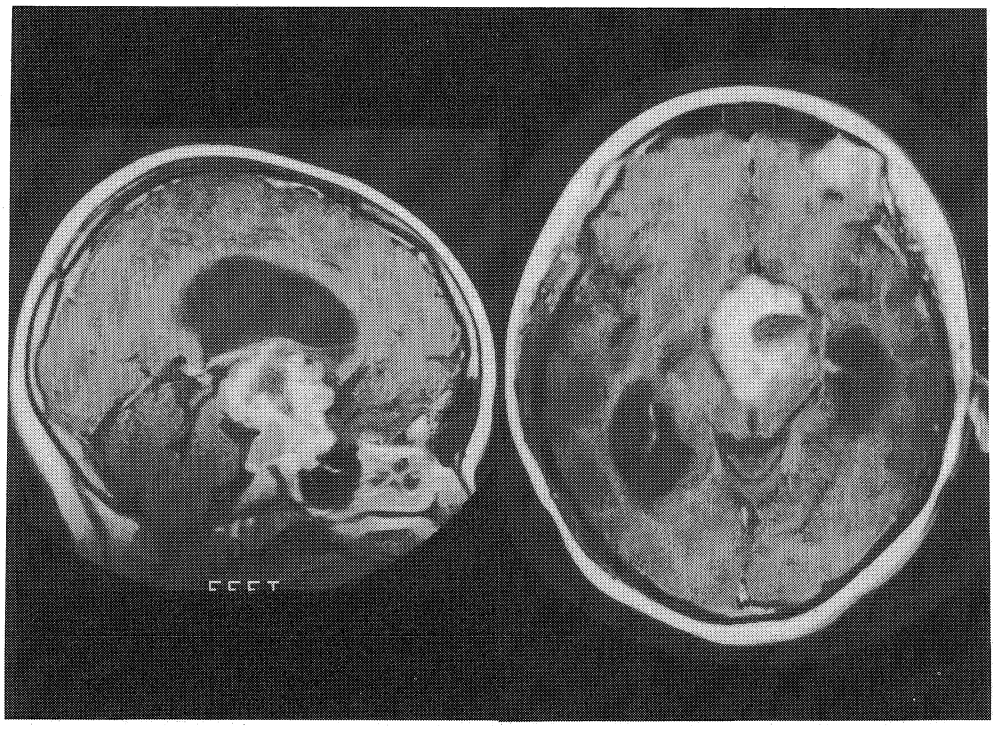

Fig. 1. MRI scan demonstrating a large tumor extending to third venricle accompanying hydrocephalus (enhanced by Gd-DTPA).

tolerance.

On Jan. 17, 1992, she showed polyuria and weight reduction triggered by a respiratory infection. Her family then gave her a large amount of soft drink containing glucose for supplement of water, which brought about gradual clouding of consciousness.

She was hospitalized on an emergency basis on Jan. 19. At the time of admission, she was drowsy and did not respond when called. Her blood pressure was 120/70 mmHg, pulse rate 86/min. and respiration rate 20/min. Her skin was slightly dry. Neurologically, no paralysis or abnormal movement of extremities were found. She was ableptic and demonstrated lateral nystagmus. The results of urine and blood chemical examination (Table 2) showed high glucose in urine and keton body trace positive. The blood glucose levels were as high as 600 mg/dl or higher. GPT, LDH, CPK and the electrolytes, Na and Cl were elevated. The plasma osmolarity (427 mOsm/L) was remarkably high. The urine osmolarity was 634 mOsm/L. HbA_1c was 10.0 %.

On the basis of these results, she was diagnosed as having fallen into HODC, for which administration of supplemental fluids and insulin was started. As shown in Fig. 2, these treatments quickly normalized the blood glucose levels. She recovered consciousness, but slightly degraded on the 4 th day, when she demonstrated hyponatremia and low plasma osmolarity. We judged it transitional to water overload state and controlled the dose of DDAVP and supplemental fluids, which successfully ameliorated the symptoms.

Insulin administration could be suspended by the 5 th day and the blood glucose maintained normal levels thereafter. The elevation of LDH and CPK seen at the time of initiation rapidly

Table 1. Pituitary function tests after removal of craniopharyngioma

I. Basal hormone values

ACTH	19.9 pg/ml	Cortisol	0.4 μg/dl
GH	0.5 ng/ml	T3	51.3 ng/dl
PRL	12.6 ng/ml	T4	3.8 μg/dl
LH	< 0.5 mIU/ml	freeT4	0.6 ng/dl
FSH	< 0.5 mIU/ml		
TSH	1.2 μU/ml	PRA	23.99 ng/ml/h
ADH	0.2 pg/ml	Aldosterone	127.6 pg/ml

II. Insulin tolerance test (4U Regular insulin i. v.)

		0'	10'	20'	30'	40'
B. glucose	(mg/dl)	98	95	66	NE	40
GH	(ng/ml)	0.4	0.4	0.5	0.5	0.5
Cortisol	(μg/dl)	2.6	NE	NE	NE	2.5

*NE : no examined

III. GRF test (100 μg i. v.)

		0'	15'	30'	60'	120'
GH	(ng/ml)	0.5	0.6	0.5	0.6	0.6

Table 2. Labolatory data ; urinary, blood chemical and blood gas analysis on admission (Jan. 19th 1992)

Urine			
pH	6.0	Ch-E	671 IU/L
Protein	(−)	T. Chol	210 mg/dl
glucose	(+++)	BUN	19 mg/dl
ketone body	(±)	Cr	0.8 mg/dl
bilirubin	(−)	Na	151 mEq/l
urobilinogen	(±)	K	3.6 mEq/l
occult blood	(−)	Cl	114 mEq/l
		glucose	>600 mg/dl
Peripheral blood			
RBC	381×10^4 /mm³	CRP	3.6 mg/dl
Hb	10.6 g/dl	HbA_{1c}	10.0 %
Ht	33.7 %	Fructosamine	440 μmol/dl
WBC	6,600 /mm³		
Pl	12.3×10^4 /mm³	Blood gas analysis	
Blood Chemistry		pH	7.41
T. Bil	2.0 mg/dl	PO_2	73 mmHg
D. Bil	0.7 mg/dl	PCO_2	32.2 mmHg
I. Bil	1.3 mg/dl	HCO_3	20.5 mmol/l
GOT	47 IU/L	B. E.	−2.8 mmol/l
GPT	19 IU/L		
LDH	1162 IU/L	Plasma and Urinaly Osmolarity	
CPK	785 IU/L	P-Osm	427 mOsm/l
		U-Osm	634 mOsm/l

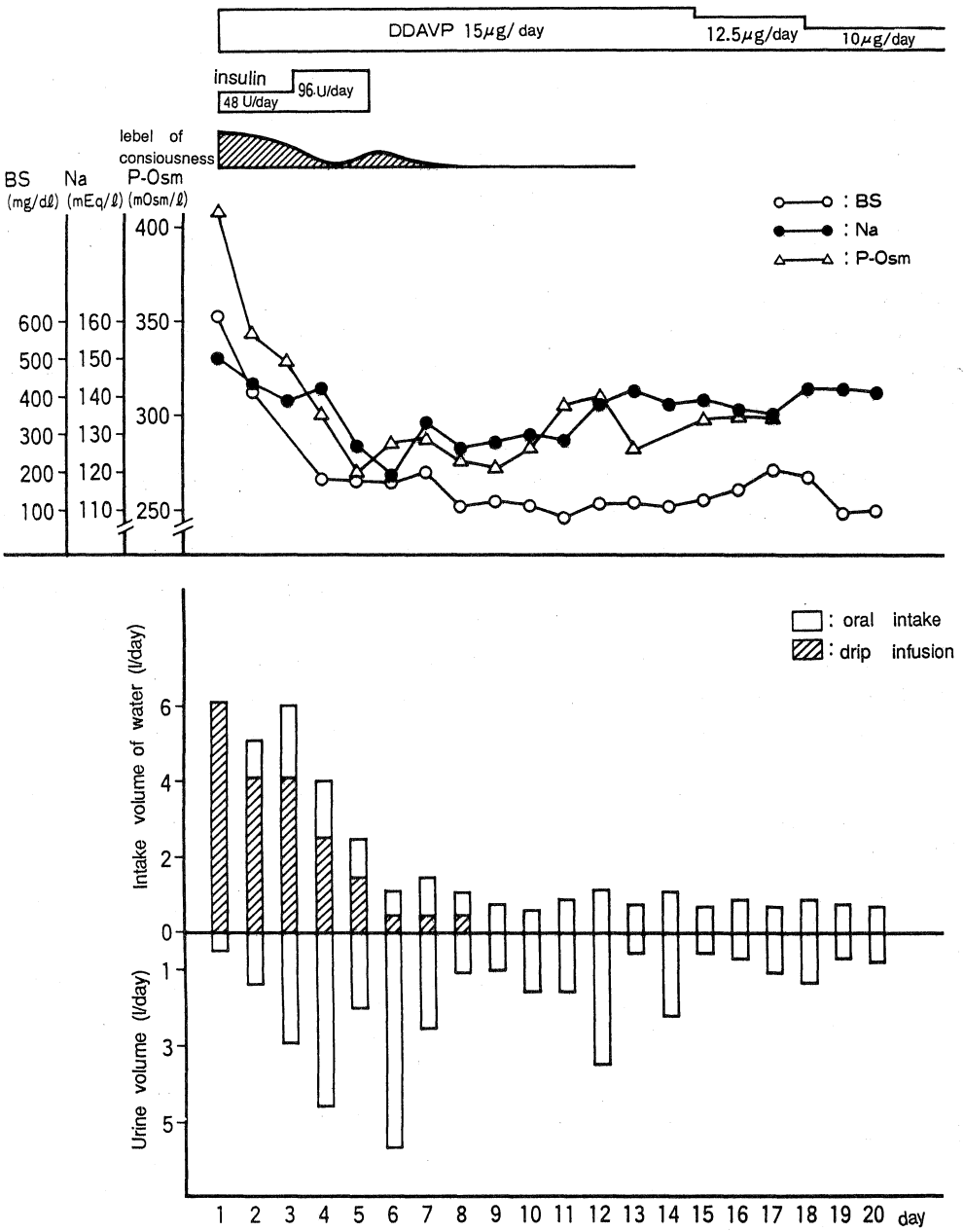

Fig. 2. The blood glucose, Na, plasma osmolarity and water balance after admission.

improved. This seemed to have been caused by rhabdomyolysis associated with HODC. One month later, 75 g OGTT showed (Table 3) a slight abnormality in glucose tolerance. However, insulin secretion was high both in basic levels and peak. Although the peak lagged, it did not reach the level of the diagnostic criteria for diabetes. Subsequently, the glucose levels maintained normal and the response to 75 gOGTT showed normal 10 months later.

Table 3. 75 g Oral glucose tolerance test after restoration from hyperosmolar diabetic coma (HODC)

I. 1 month after HODC (Feb. 7th 1992)

	0'	30'	60'	90'	120'
B. glucose(mg/dl)	90	133	178	193	194
IRI (μU/ml)	23.3	71.8	114.8	129.4	159.8

II. 10 months after HODC (Nov. 19th 1992)

	0'	30'	60'	90'	120'
B. glucose(mg/dl)	99	157	195	171	155
IRI (μg/dl)	30.1	84.6	91.3	90.8	106.3

DISCUSSION

HODC is a state of metabolic failure unaccompanied by ketoacidosis in spite of marked hyperglycemia, and is basically different in its pathogenetic mechanism from diabetic ketoacidosis. Specifically, HODC can be found in subjects without any history of diabetes prior to manifestation (6). Moreover, not a few of those cases show necessitating without any treatment for diabetes or demonstrating no abnormality in glucose tolerance after restoration.

The present patient also had no previous history of diabetes before the occurrence of HODC. It started during treatment for hypopituitarism and diabetes insipidus and diabetes was not found after the recovery. The pathogenesis of HODC in the present case is considered to be as follows (Fig. 3):

Due to her thirst disorder, she did not feel thirsty even under water deficiency. For water supplement, the necessary amount of fluid was calculated on the basis of urine volume. Under these circumstances, she demonstrated polyuria due to insufficient dosage of DDAVP. As a result of giving water by a large amount of soft drink which contained glucose, she fell into HODC. According to the mechanism shown in Fig. 3, the plasma osmolarity elevated due to the lack of DDAVP supplement and the lack of water intake, which resulted in insulin resistance in the periphery. Because of the glucose rich soft drink, hyperglycemia also accelerated dehydration and then increased insulin resistance so as to induce HODC. Two cases of diabetes insipidus associated with HODC reported by MITSUKAWA et al. (6) also did not have any history of diabetes before their manifestation. They fell into HODC upon interruption of DDAVP. It is problematic whether these cases ought to be classified according to the criteria of HODC, because they presented a transient hyperglycemia due to dehydration. We believe that HODC which accompanies transient abnormality in glucose tolerance due to dehydration should be considered as an independent entity.

Among reported cases of HODC, cases without diabetes are not few. In most of them, dehydration plays the initial role of instigator, e. g. high-calorie transfusion triggering HODC in cerebrovascular disease, burns (7) (8), or surgery, and vomiting and diarrhea sometimes producing HODC in infants (9) (10).

Let us consider the pathogenic mechanisms wherein dehydration triggers HODC:

I. induction of insulin resistance in the peripheral tissue due to elevation of plasma

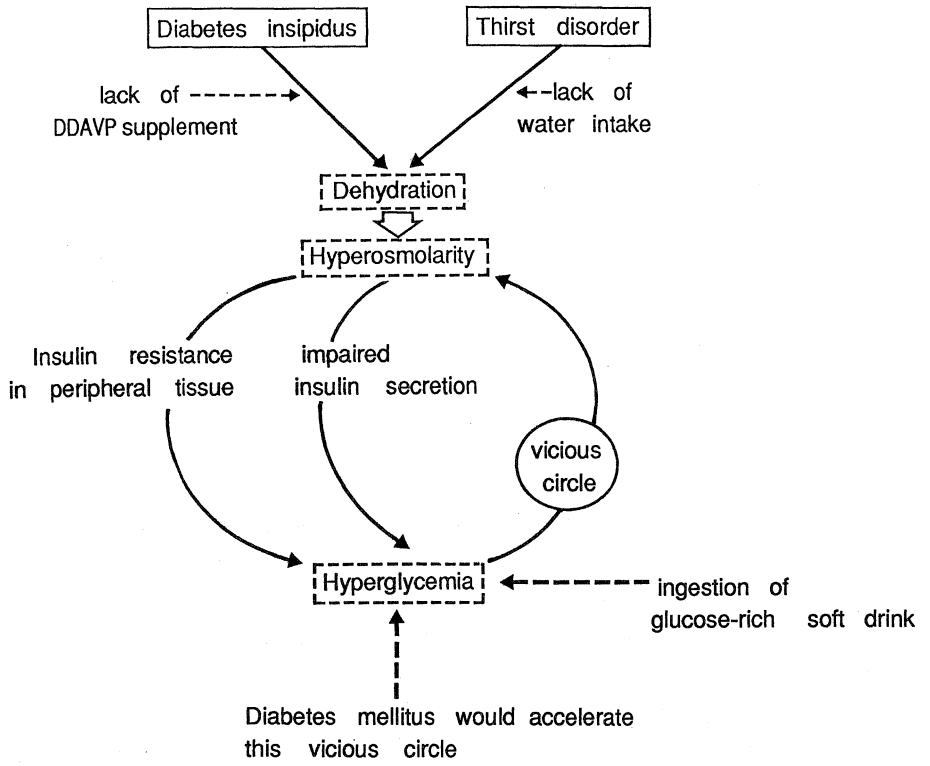

Fig. 3. Schematic presentaion of a mechanism by which this case could have fallen into hyperosmolar diabetic coma.

osmolarity (5).

II. reduction of insulin secretion due to dehydration.

III. acceleration of secretion of antagonistic hormones to insulin such as glucagon and cortisol (11).

IV. elevation of arginine vasopressin (AVP) due to dehydration and dehydration itself play a role of resistance to transition to ketoacidosis (8).

If HODC occurs by the above mechanisms, diabetes is not an indispensable factor. Rather it is easier to accept the view that diabetic cases might easily shift to become a distinct pathological entity, HODC. If diabetes may be regarded as one of the factors causing dehydration, as shown in Fig. 3, we can recognize the HODC resulting in marked hyperglycemia due to dehydration as "dehydration hyperglycemia".

Then cases with diabetes prior to HODC manifestation would be treated as "dehydration hyperglycemia with diabetes" within the same concept as HODC has heretofore been considered, while those without pre-existing diabetes would be treated simply as "dehydration hyperglycemia without diabetes".

It has been considered that the reason for ketoacidosis not occurring even with severe hyperglycema is that dehydration inhibits lipolysis (4) or that AVP inhibits production of keton bodies (12). It is clear that diabetic ketoacidosis (DKA) and dehydration hyperglycemia (DHG)

are totally different. The basic cause for DKA is an absolute deficiency of insulin. On the other hand, in DHG, there is sudden dehydration for some reason, bringing about hyperglycemia. Thus, starting from initiation, their respective pathologies are totally different.

If the HODC cases are studied based on the broad concept of "dehydration hyperglycemia", the mechanism of its manifestation is very easy to recognize. Considering the above factors, if HODC would be viewed as DHG and not as a pathology peculiar to diabetes, cases of dehydration would then be treated with an awareness of the possibility of HODC occurring.

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