δ-AMINOLEVULINIC ACID DEHYDRATASE DEFICIENCY PORPHYRIA (ADP) WITH SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH) IN A 69-YEAR-OLD WOMAN

MURAOKA, Akihiro
SUEHIRO, Itsuo
FUJII, Masatoshi [et. al.]

(Citation)
The Kobe journal of the medical sciences,41(1):23-31

(Issue Date)
1995-04

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/E0000926

Kobe J. Med. Sci. 41, 23/31, April 1995

δ-AMINOLEVULINIC ACID DEHYDRATASE DEFICIENCY PORPHYRIA (ADP) WITH SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH) IN A 69-YEAR-OLD WOMAN

Akihiro MURAOKA, Itsuo SUEHIRO, Masatoshi FUJII, and Keiji MURAKAMI

Department of Internal Medicine, Suma Red Cross Hospital, 684-1 Myohoji-Suganoike, Suma, Kobe 654-01, Japan

INDEXING WORDS

δ-aminolevulinic acid dehydratase; ALAD porphyria; SIADH; ADP

SYNOPSIS

δ-Aminolevulinic acid dehydratase deficiency porphyria (ALAD porphyria, ADP) with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in a 69-year-old woman is reported. The patient was admitted to our hospital complaining of slight cough with low-grade fever, and treated with piperacillin sodium, resulting in complete resolution of the symptoms, following a diagnosis of bronchopneumonia. Thereafter, however, she began to complain of vomiting, abdominal pain, facial numbness and paresis of the extremities with gait disturbance, and became comatose with hyponatremia (serum Na concentration 119 mEq/L) in a few days. Laboratory tests revealed an antidiuretic hormone (ADH) level of 13.5 pg/mL, plasma osmolality 218 mOsm/KgH_2O, urinary osmolality 429 mOsm/KgH_2O, urinary Na concentration $>$20 mEq/L, and no abnormalities of thyroid, adrenal or renal function. Neither edema nor dehydration was evident. These data indicated the presence of SIADH.

Received for publication : April 27, 1995
Authors' names in Japanese : 村岡章弘, 末広逸夫, 藤井正俊, 村上啓治

No abnormalities suggestive of malignant or infectious diseases such as lung cancer, pneumonia and Guillain-Barré syndrome were evident from laboratory and roentgenographic findings. As the cause of SIADH, therefore, porphyria was suspected. Metabolites and activities of enzymes in the heme biosynthetic pathway were examined, and very low activity of δ-aminolevulinic acid dehydratase (ALA-D) (0.14 μmol PBG/mL RBC/h) was found. The patient was neither an alcoholic nor a heavy smoker, and she had no past history of heavy metal intoxication, photosensitivity or tyrosinemia.

On the basis of these data and clinical features, she was diagnosed as having ADP. We consider this to be the first case of ADP reported in Japan.

INTRODUCTION

Porphyria is a disease caused by deficiency of enzymes in the heme biosynthetic pathway. Generally, it is characterized by marked elevation of both the plasma and urinary concentrations of porphyrin precursors such as δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) during acute attacks. Among the porphyrias, δ-aminolevulinic acid dehydratase (ALA-D) deficiency porphyria (ADP) caused by a defect of ALA-D, which is the second enzyme in the heme pathway, is recognized to be a very rare congenital disease.

Although the symptoms of this disease are variable, as in other acute porphyrias, it is characterized by no increase of urinary PBG during the acute phase. In this paper we present the first reported case of ADP in Japan.

CASE REPORT

A 69-year-old woman was admitted complaining of slight cough and low-grade fever on July 17, 1994, with no history of medication. Laboratory data on admission included a white blood cell (WBC) count of 3900 /μL, a C-reactive protein (CRP) level of 8.7 mg/dL and an erythrocyte sedimentation rate (ESR) of 24 mm/h (Table 1). X-ray examination showed a segmental infiltrate without a visible air bronchogram in the right lower lung field. The patient

Table I. Laboratory data on admission.

Peripheral blood			
White blood cell count	3900/μl	Total cholesterol	121 mg/dl
Red blood cell count	410×10^4/μl	Triglycerides	76 mg/dl
Hemoglobin	11.8 g/dl	Aspartate aminotransferase	24 IU/l
Hematocrit	35.6 %	Alanine aminotransferase	29 IU/l
Platelet	13.3×10^4/fl	Lactate dehydrogenase	443 IU/l
Erythrocyte sedimentation rate	24 mm/h	Alkaline phosphatase	179 IU/l
Blood chemistry		γ-Glutamyltranspeptidase	18 IU/l
Total protein	6.8 g/dl	Cholinesterase	0.75 ΔPH
Albumin	4.0 g/dl	Total bilirubin	0.9 mg/dl
A/G ratio	1.43	Amylase	60 IU/l
Na	137 mEq/l	C-reactive protein	8.7 mg/dl
K	3.62 mEq/l	Fasting plasma glucose	94 mg/dl
Cl	101 mEq/l		
Ca	7.8 mg/dl		
P	3.3 mg/dl		
Blood urea nitrogen	15.2 mg/dl		
Creatinine	1.3 mg/dl		
Uric acid	5.2 mg/dl		

was diagnosed as having bronchopneumonia, and treated with piperacillin sodium (1g× 2/day), resulting in improvement.

From July 28, however, she developed vomiting, abdominal pain , facial numbness and paresis of the extremities with gait disturbance. These symptoms started with vomiting and abdominal pain, followed by neuropathy. Her sensorium and speech content showed progressive deterioration of the level of consciousness, being inattentive and unable to perceive all elements of her situation.

On August 1, she became comatose with hyponatremia (serum Na concentration 119 mEq/L). Laboratory tests on August 3 (Table 2) showed a serum antidiuretic hormone (ADH) level of 13.5 pg/mL, plasma osmolality 218 mOsm/KgH_2O, urinary osmolality 429 mOsm/KgH_2O, urinary Na concentration >20 mEq/L, and no abnormalities of thyroid, adrenal or renal function. Neither edema nor dehydra-

Table II. Laboratory data on SIADH and porphyria.

	8/3	8/9	8/29	normal range
Urine: coproporphyrin		306	40	<180 μg/day
uroporphyrin		<1.8	–	<20 μg/day
porphobilinogen		0.36	–	<2.0 mg/day
δ-aminolevulinic acid		12.24	3.6	<5.0 mg/day
Blood: erythrocyte protoporphyrin		48	–	<100 μg/dl RBC
δ-aminolevulinic acid dehydratase activity		0.14	0.14	0.47-2.31 μmolPBG/ml RBC/h
porphobilinogen deaminase activity		47.9	–	38-74 nmol URO/ml RBC/h
antidiuretic hormone	13.5	–	1.9	0.3-3.5 pg/ml
lead level	–	4	–	<20 μg/dl
Osmolality				
plasma	218	–	267	276-292 mOSM/KgH_2O
urinary	429	–	441	>850 mOSM/KgH_2O

tion was evident. These data revealed the presence of the syndrome of inappropriate secretion of ADH (SIADH), which was treated by sodium supplementation or restriction of fluid intake to within 1000 mL daily. No abnormalities were detected by ultrasonography of the abdomen and computed tomography of the head and chest, and laboratory data excluded the presence of malignant or infectious diseases such as lung cancer, pneumonia and Guillain-Barré syndrome.

As the cause of SIADH, therefore, porphyria was suspected because of several symptoms specific to organs of the digestive and nervous systems. Metabolites and activities of enzymes in the heme biosynthetic pathway examined on August 9 were urinary porphobilinogen 0.36 mg/day, urinary δ-aminolevulinic acid (ALA) 12.24

mg/day, urinary coproporphyrin 306 μg/day, urinary uroporphyrin <1.8 μg/day, erythrocyte protoporphyrin 48 μg/dL RBC, δ-ALA dehydratase (ALA-D) activity 0.14 μmol PBG/mL RBC/h, porphobilinogen deaminase (PBG-D) activity 47.9 nmol URO/mL RBC/h and blood lead level 4 μg/dL (Table 2).

The analytical methods used were as follows:

(1) For coproporphyrin and uroporphyrin in urine: Shwartz method (13)
(2) For protoporphyrin in erythrocytes: Niinuma method (10)
(3) For PBG and ALA in urine: Mauzerall-Granick method (9)
(4) For ALA-D activity in erythrocytes: Sassa method (12)
(5) For PBG-D activity in erythrocytes: Kondo method (8)

The patient was neither an alcoholic nor a heavy smoker and had normal liver function. There was no past history of heavy metal intoxication, photosensitivity and tyrosinemia. Based on these data and the clinical features, she was diagnosed as having ADP.

Only by palliative treatment was a gradual improvement of complaints such as abdominal pain and neuropathy achieved. Laboratory parameters related to porphyria were reexamined on August 29, and all were within the normal ranges except for ALA-D activity (urinary δ-ALA 3.6 mg/day, urinary coproporphyrin 40 μg/day, serum ADH 1.9 pg/mL, ALA-D activity 0.14 μmol PBG/mL RBC/h) (Table 2).

DISCUSSION

Only four cases of δ-aminolevulinic acid dehydratase deficiency porphyria (ADP), which was recently established as a clinical entity, have been reported to date (Table 3) from Germany, Germany, Sweden and Belgium, respectively (2,3,5,14). All the patients were men. In the heme biosynthetic pathway, ALA-D is the second enzyme which catalyzes the condensation of two molecules of ALA to form porphobilinogen (PBG) (12) (Fig.1), and its activity in a normal state is too high to be associated with disturbances of heme biosynthesis caused by partial deficiency (≦ 50%) of the enzyme (1). Recently several mutations in the ALA-D gene have been recognized (G133R, R240W, A274T, V275M), and the possibility that ADP is caused by these mutations has been suggested (6,7,11). The G133R mutation reduces both the activity and half-life of the en-

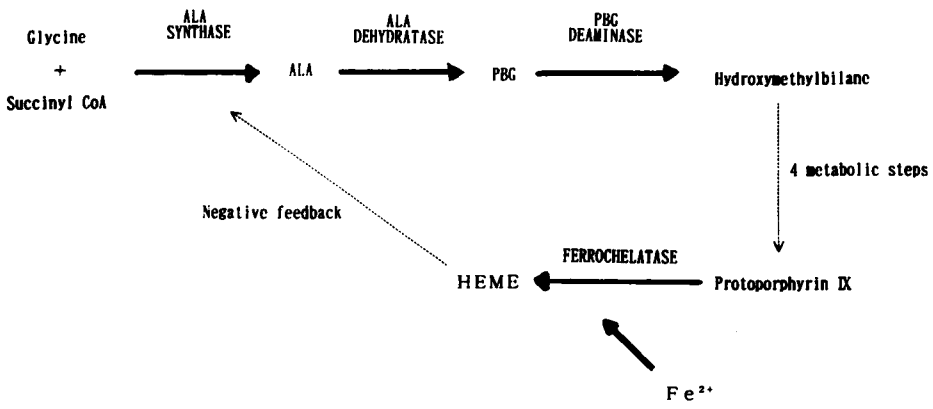

Figure 1. Heme biosynthetic pathway. (ALA, δ-aminolevulinic acid; PBG, porphobilinogen.)

zyme, the V275M mutation decreases the half-life, the R240W mutation reduces the activity but a normal half-life is maintained and the enzyme with the A274T mutation shows a markedly reduced half-life with 50 % of the normal activity (4,7,11).

Compared to homozygotes of these mutations, heterozygous carriers of this disease generally have a tendency to show no clinical symptoms unless they are triggered by influences such as infection and administration of chemicals capable of accelerating the rate of heme synthesis (4,7). Clinical symptoms in the four reported homozygous cases were variable from the viewpoint of age at onset and severity of clinical manifestations (2,3,5,14), probably depending on the amount of residual ALA-D activity (Table 3).

In our present case, moderate symptoms of the digestive system, mild sensory impairment and severe motor paresis occurred, together with disturbance of consciousness with SIADH.

SIADH occurs occasionally in patients with not only a variety

Table Ⅲ. Review of the reported cases of δ-aminolevulinic acid dehydratase deficiency porphyria.

Case	Author	Age	Sex	Nationality	Clinical features
1.	Doss et al(1979)	21	male	Germany	abdominal pain, neuropathy
2.	Doss et al(1979)	23	male	Germany	abdominal pain, neuropathy
3.	Thunell et al(1987)	3	male	Sweden	severe polyneuropathy
4.	Hassoun et al(1989)	63	male	Belgium	polyneuropathy, polycythemia
5.	Present case	69	female	Japan	neuropathy, SIADH, vomiting

of neoplasms but also various disorders of the central nervous system such as encephalitis, meningitis and acute porphyria. In acute porphyria, it is speculated that ADH is secreted in response to direct stimulation of the hypothalamic osmoreceptors, unlike ectopic ADH-producing tumors.

SIADH, which is often detected in acute intermittent porphyria (AIP), could have been caused by ADP in our case, though no case of ADP with SIADH has been reported. ALA-D activity in our patient might have decreased consistently since her birth, and to our knowledge clinical symptoms suggestive of porphyria had never become evident until the age of 69. The lower levels of urinary ALA and coproporphyrin in this patient compared to the cases reported previously might have been due to the delayed measurement after the acute phase of ADP (Table 2). ADP in our patient, therefore, was suggested to be not heterozygous but a late-onset homozygous form of ADP similar to the Belgian case (Table 3) with known or unknown mutations in the ALA-D gene because of the low activity of ALA-D (1,5).

In a hereditary disease like ADP, which is considered to be transmitted by autosomal recessive inheritance, it is generally important to investigate the familial background. The patient, who was an only daughter and whose parents had already died, had three sons and two daughters. However, no endocrinological or neurological disorder similar to the patient's has been found in any other family member.

Unfortunately, further investigations such as a pedigree study and a molecular analysis of the ALA-D gene in the patient could not be performed because of her private wishes.

REFERENCES

1. Bird, T.D., Hamernyik, P., Nutter, J.Y., and Labbe, R.F.: Am. J. Hum. Genet. 1979. 31. 662/668. Inherited deficiency of delta-aminolevulinic acid dehydratase.
2. Doss, M., Tiepermann, R.V., Schneider, J., and Schmid, H.: Klin. Wochenschr. 1979. 57. 1123/1127. New type of hepatic porphyria with porphobilinogen synthase defect and intermittent acute clinical manifestation.
3. Doss, M., Tiepermann, R.V., and Schneider, J.: Int. J. Biochem. 1980. 12. 823/826. Acute hepatic porphyria syndrome with porphobilinogen synthase defect.
4. Fujita, H., Sassa, S., Lundgren, J., Holmberg, L., Thunell, S., and Kappas, A.: Pediatrics 1987. 80 (6). 880/885. Enzymatic defect in a child with hereditary hepatic porphyria due to homozygous δ-aminolevulinic acid dehydratase deficiency: immunochemical studies.
5. Hassoun, A., Verstraeten, L., Mercelis, R., and Martin, J-J.: J. Clin. Chem. Clin. Biochem. 1989. 27. 781/786. Biochemical diagnosis of an hereditary aminolaevulinate dehydratase deficiency in a 63-year-old man.
6. Ishida, N., Fujita, H., Noguchi, T., Doss, M., Kappas, A., and Sassa, S.: Biochem. Biophys. Res. Commun. 1990. 172. 237/242. Message amplification phenotyping of an inherited δ-aminolevulinate dehydratase deficiency in a family with acute hepatic porphyria.
7. Ishida, N., Fujita, H., Fukuda, Y., Noguchi, T., Doss, M., Kappas, A., and Sassa, S.: J. Clin. Invest. 1992. 89. 1431/1437. Cloning and expression of the defective genes from a patient with δ-aminolevulinate dehydratase porphyria.
8. Kondo, M., Mori, M., and Aoki, Y.: Acta. Haematol. Jpn. 1990. 53. 851/859. Increased porphobilinogen deaminase activity and protoporphyrin content in erythrocytes of patients with primary acquired sideroblastic anemia.
9. Mauzerall, O., and Granick, S.: J. Biol. Chem. 1956. 219. 435/446. The occurrence and determination of δ-aminolevulinic acid and porphobilinogen in urine.
10. Niinuma, Y., Sakai, T., Yanagihara, S., and Ushio, K.: Jpn. J.

Ind. Health 1981. 23. 254/259. A modified FEP (free erythrocyte protoporphyrin) test.

11. Plewinska, M., Thunell, S., Holmberg, L., Wetmur, J.G., and Desnick, R.J.: Am. J. Hum. Genet. 1991. 49. 167/174. δ-aminolevulinate dehydratase deficient porphyria: identification of the molecular lesions in a severely affected homozygote.
12. Sassa, S.: Enzyme 1982. 28. 133/145. δ-aminolevulinic acid dehydratase assay.
13. Shwartz, S., Edmondson, P., Stephenson, B., Sarkar, D., and Freyholtz, H.: Ann. Clin. Res. 1976. 9 (suppl.17) 156/161. Direct spectrophotometric determination of porphyrin in diluted urine.
14. Thunell, S., Holmberg, L., and Lundgren, J.: J. Clin. Chem. Clin. Biochem. 1987. 25. 5/14. Aminolaevulinate dehydratase porphyria in infancy. A clinical and biochemical study.