False-Positive Accumulation of Metaiodobenzylguanidine in a Case with Acute Intermittent Porphyria

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Abstract

We report a 36-year-old woman presenting with hypertensive encephalopathy followed by bulbar palsy and quadriplegia. After an extensive screening for secondary causes of hypertension, the patient was suspected of having pheochromocytoma due to increased levels of catecholamines in the plasma and the urine, and positive ¹³¹I-metaiodobenzylguanidine (MIBG) accumulation in the gallbladder. However, MIBG accumulation was not reproducible without any tumors accompanying this accumulation in the gallbladder. A diagnosis of acute intermittent porphyria was finally confirmed based on the characteristic pictures, increased urinary excretion of porphobilinogen, and identification of a heterozygous missense mutation of R173W in the hydroxymethylbilane synthase gene. This case highlights a pitfall in utilizing MIBG to detect a source of excessive catecholamine and also suggests the importance of having a complete clinical history and extensive work-up of any possible differential diagnosis. We also review the potential mechanism by which false-positive MIBG accumulation occurs.

Key words: acute intermittent porphyria, MIBG, pheochromocytoma, false-positive


Introduction

Metaiodobenzylguanidine (MIBG) has been widely used as a clinical tool to detect and localize pheochromocytoma since MIBG selectively accumulates in cells derived of neuroectodermal origin, including pheochromocytoma (1). It has been shown that the specificity of MIBG accumulation, when used to localize clinical pheochromocytomas, is as high as 95-100% (2). Reflecting excessive secretion of catecholamines from tumors, clinical symptoms seen in patients with pheochromocytoma are headache, anxiety, weight loss, nausea, and paroxysmal hypertension.

Acute intermittent porphyria (AIP) is characterized by episodic acute attacks of abdominal pain, headache, paroxysmal hypertension, seizures, confusion and hallucinations. Acute porphyria attacks can be life-threatening, since the motor polyneuropathy occasionally progresses to respiratory failure requiring a mechanical ventilator. Patients suffering from AIP, however, can be totally asymptomatic during the remission periods. This is because AIP is caused by reduced enzyme activity of hydroxymethylbilane synthase involving the heme biosynthesis, and excessive accumulation of neurotoxic heme precursors is only seen during and shortly after the attacks.

As described above, there is an overlap between such clinical symptoms of AIP and those of pheochromocytoma as paroxysmal hypertension and headache, and thus patients with AIP can be misdiagnosed with pheochromocytoma or vice versa. Here, we report a case of AIP with a confusing finding of false-positive MIBG accumulation suggesting pheochromocytoma. We also review the putative mechanisms involved in the false-positive MIBG accumulation.
Case Report

A 36-year-old woman was admitted to the regional hospital in our area because of acute onset of visual field loss caused by hypertensive encephalopathy. While her visual field loss gradually improved by vigorous anti-hypertensive treatment, she developed progressive quadriplegia and bulbar paralysis and was therefore transferred to our university hospital. Her past medical history was unremarkable except for generalized body pain associated with paroxysmal hypertension during the premenstrual period for more than ten years.

On physical examination, she was dehydrated and urinating port wine-colored urine. Additionally, there was apparent bulbar paralysis and quadriplegia associated with a loss of deep tendon reflexes. Since the patient was intubated and under sedation, we were not able to ask her whether she had sensation in her limbs. A blood test showed moderate anemia and the anti-ganglioside antibodies studied were negative. Cerebrospinal fluid analysis was normal. Nerve conduction study in the median, ulnar, peroneal, and tibial nerve showed normal conduction velocity with a low amplitude and velocity was 0.79 mV and 44.0 m/sec in the median nerve and 1.5 mV and 46.4 m/sec in the ulnar) indicating axonal motor polyneuropathy while there was no involvement of sensory nerves. From the clinical picture of the patient, we strongly suspected an attack of acute porphyria. This was supported by a markedly elevated urinary concentration of porphobilinogen (134.2 mg/day; reference range less than 2 mg/day). Other urinary porphyrins were also increased; 5-aminolevulinic acid (22.3 mg/L; reference range <5 mg/L), uroporphyrin (1.820 μg/gCr; reference range <36 μg/gCr) and coproporphyrin (8.540 μg/gCr; reference range 170 μg/gCr). After obtaining written informed consent from the patient and her family and approval from the ethical committee at Tottori University Hospital (Tottori, Japan), we were also able to detect a heterozygous mutation in the hydroxymethylbilane synthase gene (R173W caused by 517C to T in exon 10), which confirmed the diagnosis of AIP (Fig. 1A). There was an additional polymorphism of 606 G to T (Fig. 1A), and genetic testing of her family members revealed that the disease allele was paternally inherited (Fig. 1B). The patient was treated with intravenous hyperalimentation, cimetidine, and chlorpromazine, and the neurological signs and symptoms gradually improved.

Before being transferred to our hospital, the patient was extensively investigated for the possibility of secondary hypertension as an etiology of hypertensive encephalopathy. Plasma levels of catecholamines and urinary levels of catecholamine metabolites were found to be elevated: plasma adrenaline (242 pg/mL; reference range <100 pg/mL), noradrenaline (2,583 pg/mL; reference range 100 to 450 pg/mL), dopamine (231 pg/mL; reference range <20 pg/mL) and urinary metanephrine (0.22 mg/day; reference range 0.04 to 0.19 mg/day), normetanephrine (1.37 mg/day; reference range 0.09 to 0.33 mg/day), VMA (9.0 mg/day; reference range 1.5 to 4.3 mg/day). Therefore, a diagnosis of pheochromocytoma was considered and 123I-MIBG scintigraphy showed positive accumulation in the gallbladder (Fig. 2A, 2B). However, we were not able to find any tumorous lesions in or near the gallbladder by ultrasound (Fig. 2C). 123I-MIBG accumulation studied 14 days after the 123I-MIBG study showed no accumulation of MIBG in the gallbladder or adrenal gland (Fig. 2D), and there was a gradual decrease of urinary metanephrine.

Discussion

The case reported here was first presented with hypertensive encephalopathy caused by paroxysmal hypertension subsequently complicated with bulbar palsy and quadriplegia as a result of axonal motor polyneuropathy. The diagnosis of AIP was made based on the characteristic clinical presentation, increased urinary excretion of porphobilinogen, and genetic testing. It has been shown that mutations were widely distributed within the gene coding hydroxymethylbilane synthase, and the mutation identified in the present patient was also observed in Caucasians as well as in other unrelated Japanese patients with AIP (3-5). It has also been shown that the mutation is the substitution of an essential arginine to tryptophan in the active site of the enzyme, decreasing catalytic activity (<1%) (6). The patient could have been incorrectly diagnosed with pheochromocytoma based on her paroxysmal hypertension and false-positive accumulation of 123I-MIBG. A misdiagnosis of this kind can easily occur in
Japan, where AIP is extremely rare [up to 198 cases of AIP have been diagnosed as of 2009 (7)]. In addition, the clinical presentation of pheochromocytoma can vary greatly and mimic signs and symptoms seen in many other disorders (2).

It has been shown that acute porphyria attacks are commonly seen in females, although very rarely before puberty and after menopause, with a peak occurrence within the third decade (8, 9). Most patients have one or two attacks and then fully recover without a recurrence for the rest of their lives, but less than 10% develop recurrent acute attacks. During the acute attacks, reflecting augmented sympathetic activity, tachycardia, excessive sweating, and hypertension are commonly present (10). As shown herein, increased catecholamine production can be detected and may possibly suggest an incorrect diagnosis. When an acute attack of porphyria is suspected, it is essential to obtain a complete clinical history, perform an extensive work up of any possible differentiating diagnosis, and determine the urinary concentration of porphobilinogen (11).

MIBG is a norepinephrine analogue which is taken up by neuroendocrine cells through an active mechanism and stored in the neurosecretory granules. This leads to a specific concentration of the molecule in the neuroendocrine cells (1). Only limited reports of false-positive uptake in other lesions have been published. One major cause of false-positive findings is urinary tract retention, since the reagent is excreted in the urine (12). Other rare false-positive MIBG accumulations have been reported in the adrenal gland with adenoma (13), carcinoma (14) or metastatic choriocarcinoma, and adenomatous polyp of the cecum, infantile myofibromatosis (15), pancreatoblastoma (15), acute focal pyelonephritis, hepatic hemangioma, hepatocellular carcinoma (16), and juvenile capillary hemangioma (17). The non-specific accumulation of MIBG is thought to be mediated by a passive uptake and diffusion. It has been shown that non-specific uptake tends to disappear more rapidly than specific uptake (15). An augmented blood flow and enhanced diffusion of MIBG within the tumor could be putative mechanisms of false-positive MIBG uptake and accumulation in non-neuroendocrine tumors (15, 18).

There was false-positive accumulation of MIBG in the gallbladder in the case with AIP reported here. To our knowledge, there is no report of a similar false-positive MIBG accumulation. The accumulation of MIBG in the gallbladder can be considered a characteristic finding in patients with AIP. Since the liver is one of the major organs involving heme biosynthesis, which is partially defective in AIP, MIBG clearance might be disturbed during acute attacks of AIP. It is not known whether MIBG accumulates in any specific organ in patients with AIP. False-positive MIBG accumulation in the normal adrenal gland in a patient with AIP has in fact been reported (19). Thus, it seems unlikely that MIBG tends to accumulate in the gallbladder in AIP although there have been no studies confirming this. The other possibility is that the critical condition of the patient reported herein might have influenced the blood flow of the gallbladder, as the patient was severely ill and receiving intravenous hyperalimentation when 131I-MIBG accumulation was studied. We were not able to find any studies on the blood flow of the gallbladder in patients with intravenous hyperalimentation, in which the gallbladder is known to dilate. However, the increased blood flow in the gallbladder would not have been the cause of false-positive MIBG accumu-

Figure 2. False-positive accumulation of MIBG in the gallbladder. There is clear accumulation of 131I-MIBG in the right upper abdomen (A), which corresponds to the gallbladder, as shown in SPECT (B). There was no detectable tumor in or near the gallbladder on ultrasound (C). 123I-MIBG scintigraphy taken 14 days after 131I-MIBG showed no abnormal accumulation (D).
mulation since the patient was still under intravenous hyper-
alimentation when $^{123}$I-MIBG scintigraphy was studied.

In conclusion, an acute attack of porphyria should be con-
sidered when female patients of reproductive age present
with characteristic episodes of neurovisceral symptoms.
However, the present patient could have been incorrectly di-
agnosed with pheochromocytoma based on MIBG accumu-
lation in the gallbladder. The possibility of a false-positive
MIBG accumulation should always be taken into considera-
tion when using MIBG scintigraphy to detect a
catecholamine-secreting tumor, or the result of the MIBG
can be misleading.

Author’s disclosure of potential Conflicts of Interest (COI).
Astushi Kawakami: Research funding, Ministry of Health, Labor
and Welfare of Japan.

Acknowledgement
The first two authors (T.M., and R.O.) contributed equally to
this report.

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