

Acute Intermittent Porphyria: Psychosis as the Only Clinical Manifestation

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Abstract: Acute intermittent porphyria (AIP) is the most common of the four forms of neuroporphyria. AIP mimics a variety of disorders and thus poses a diagnostic quagmire. Abdominal pain occurs in 90-95% of the attacks. Some patients develop psychiatric symptoms such as psychosis similar to schizophrenia. The diagnostic difficulty may lead to under-diagnosis of patients who present with strictly psychiatric symptoms. This assumption is supported by a high prevalence of AIP in psychiatric hospitals. Therefore, we encourage a high index of suspicion for AIP in psychiatric patients in order to prevent false psychiatric diagnosis. In addition we discuss psychotropic drugs that may exacerbate acute attacks in undiagnosed patients. We report a case in which the diagnosis of AIP was clouded by the presence of only psychiatric symptoms. The clue for diagnosis was an anamnestic detail of the use of a porphrogenic drug prior to the admission. The diagnosis of AIP was supported by excess of alpha aminolevulinic acid (ALA) and porphobilinogen (PBG) in urine concomitantly with a decrease in porphobilinogen deaminase (PBGD) activity in erythrocytes. The diagnosis was further strengthened by the fact that the patient's father was identified as an AIP carrier. However, in the absence of typical organic symptoms of porphyria, one cannot definitely rule out the presence of schizophrenia in this patient in addition to AIP.

Introduction

Acute porphyrias comprise a group of four disorders of the heme biosynthetic pathway, which differ biochemically, but share similar clinical neuropsychiatric symptoms (1-3). The course of the diseases consists of an acute and a latent phase. Various combinations of the following symptoms characterize the former: abdominal pain, peripheral neuropathy, autonomic dysfunction and psychiatric symptoms such as psychosis, anxiety, depression, agitation and delirium (2-4). Acute attacks are most common during the second to fourth decades and are often triggered by exposure to exogenous precipitating factors, mainly drugs. Factors such as alcohol, cigarette smoking, fasting, stress and infection have also been implicated (1-3). Delay in diagnosis may cause serious neurological and mental sequelae and may even lead to mortality (2, 4). The most common form of neuroporphyrias is acute intermittent porphyria (AIP), caused by deficiency of porphobilinogen deaminase (PBGD). It is inherited in an autosomal dominant manner with incomplete

penetrance. Only 10% of AIP gene carriers develop the clinical syndrome (1, 2). In most European countries, the estimated prevalence of clinically overt acute porphyria is 1-2 in 100,000. Most of these individuals have AIP (2). A higher frequency of AIP was reported in patients with psychiatric illness (5). The following case of AIP exemplifies the importance of considering neuroporphyria in the differential diagnosis of psychiatric patients.

Case report

Mr. M. is a 32-year-old male. Four years prior to his admission he developed a growing interest in religion and became an orthodox Jew. He has been working in technical support for a software company for the past few years. Apart from hypertension of unknown origin since the age of 22, he has been healthy, with no psychiatric history. His family's psychiatric history is negative.

He was admitted to hospital due to a sudden acute psychosis that lasted for three days. A mental

status examination indicated he had persecutory delusions as well as erotomanic delusions towards a girl he once knew. He had experienced thought broadcasting from that girl and had auditory and visual hallucinations of her. He was very violent and unpredictable. His family reported that he had taken sulphonamides about 10 days before his admission due to urethritis. The antibiotics caused a rash on his left arm, face and penis. He denied the use of narcotics or alcohol.

Physical and neurological examinations on his arrival were normal except for mild hypertension. Extensive laboratory studies were also unremarkable. A urine test for drugs was negative. He had undergone a computed tomography (CT) of the head three months earlier due to headaches, which was normal.

Mr. M. was treated with IM perphenazine up to 15 mg/day and later with perphenazine PO, up to 24 mg/day. Two weeks later perphenazine was replaced by risperidone up to 4 mg/day, due to extrapyramidal side effects. A week after his admission, his erotomanic delusions and his hallucinations disappeared.

Although he did not have any physical complaints, the fact that he took sulphonamides a few days prior to the development of the psychotic state, which lasted only a week, raised the suspicion of an acute porphyria attack, since sulphonamides are considered porphyrogenic drugs (1). Moreover, he

had suffered from chronic hypertension, which is a well-known complication of AIP. It affects 50-60% of the patients in the acute phase and 30% in the latent phase (6). Two weeks after resolution of symptoms, his urine, feces and blood were tested for the four acute porphyrias. It was concluded that he had undergone an acute attack of AIP. The conclusion was based on the following findings: increased urinary aminolevulinic acid (ALA), porphobilinogen (PBG) and porphyrins (Uroporphyrin, Coproporphyrin I, Coproporphyrin III) (Table I), normal fecal porphyrins (not shown), borderline activity of erythrocyte PBGD (Table I) and a small peaking of the fluorometric scan of plasma at ~404/622 nm (not shown).

Three weeks after his admission Mr. M. was discharged with instructions to continue taking 4 mg./day of risperidone on a daily basis. His follow up continued at an ambulatory psychiatric clinic and in the porphyria reference laboratory. Since AIP is inherited as an autosomal dominant condition, Mr. M.'s parents were tested for the disease and his father was found to be an AIP carrier. Both patient and family were given counseling on ways to prevent acute attacks. In the following months Mr. M. reached full remission and the risperidone was tapered gradually until he received 1 mg a week. He had no psychotic symptoms and was back working in his profession.

Table I. Various urinary and erythrocyte parameters of a 32-year-old AIP patient

parameter	Normal values	1 month after 1 st AA	2 months after 1 st AA	3 months after 1 st AA	2 nd AA
Urine ALA	< 5 mg ^a	13.9	9	12.8	14.6
Urine PBG	< 2 mg ^a	8.1	5	5.2	5.9
Urine Uroporphyrin	< 30 µg ^a	40	15	10	25
Urine Coproporphyrin I	< 60 µg ^a	166	112	96	120
Urine Coproporphyrin III	< 180 µg ^a	518	267	246	252
PBGD activity in erythrocytes	> 70%	69%	54%	ND	71%

AA — Acute attack

ND — not determined

^a — per 24 hours

Ten months after his discharge, Mr. M. was hospitalized in a psychotic state that had started abruptly a few days earlier. His parents indicated that just prior to hospitalization he had decided to get married and had also started a new job which caused him a lot of stress. There was no history of ingesting porphyrogenic drugs. He had moderately elevated urine ALA and PBG and a borderline activity of erythrocyte PBGD (Table I). The dosage of risperdone was increased to 3 mg. per day. After three days the symptoms subsided and he was discharged. In the past year, since his discharge, Mr. M. has returned to working in his profession and does not exhibit any psychiatric symptoms. He continues his follow up in an ambulatory psychiatric clinic.

Discussion

Neuroporphyrrias mimic a variety of commonly occurring disorders and thus the probability for misdiagnosis is increased (1). This case report is an example of exacerbation of AIP in which the diagnosis was clouded by the presence of solely psychiatric symptoms. The differential diagnosis included schizophrenia. However, the abrupt onset of symptoms and the quick resolution of the psychotic states combined with the findings in the patient's urine, feces and blood led to the establishment of the diagnosis of AIP. This diagnosis was further strengthened by the identification of the patient's father as an AIP carrier.

The main laboratory findings supporting the diagnosis of AIP are a decrease in PBGD activity in erythrocytes concomitantly with a 1.5-3 fold increase in urinary PBG (5). However, it was shown that the activity of the deficient enzyme PBGD is induced during acute attacks and may reach normal values during such attacks (7). In accordance with the above, a borderline activity of PBGD was recorded one month after the first attack, as well as during the second episode.. Two months after the first attack, when the patient was already in his latent phase, there was a 46% decrease in PBGD activity (Table I). A similar trend was demonstrated with regards to urinary ALA and PBG in the two month following the first attack (Table I). In addition, at the time of the patient's second admission urine samples were taken during an acute attack, immediately at his

arrival. As expected the levels of urine ALA and PBG were increased (Table I). These findings led us to the diagnosis of AIP. It seems that exposure of the patient's brain to metabolic abnormalities caused the clinical features of psychotic states (1). Still, one cannot rule out completely the presence of schizophrenia in this patient, in addition to AIP.

Severe abdominal pain, the predominant and usually the initial symptom in attacks of AIP, occurs in 90-95% of the attacks (8). This high correlation between abdominal pains and AIP may lead to ruling out AIP in any case where abdominal pains are absent. However, there are cases of acute attacks without abdominal pain (3,8). Andersson et al. describe a 45 year old woman having an attack of AIP which manifested itself only by extensor paresis in the arms, not accompanied by abdominal pain. The only precipitating factor which was identified in this case was physical exercise (8). Mr. M. did not complain of abdominal pain either prior to or during his admissions or in the past. Therefore, following this criterion would have led to misdiagnosis of a number of cases, including that of our patient.

Among patients suffering from acute porphyria, 20-58% have neuropsychiatric symptoms during acute exacerbations (1, 3). Most of the larger case series have been undertaken by neurologists or internists and therefore "mental symptoms" are not fully characterized and their prevalence is likely to have been underestimated. The psychiatric literature on AIP is comprised mostly of single case reports and small series, reporting patients experiencing almost every psychiatric symptom. Some patients, like our case, develop psychosis similar to schizophrenia (4, 9). Goldberg and Stinnett present a case of typical schizophrenia in a 27 year old male which was subsequently diagnosed as AIP. He was admitted with hallucinations, abdominal pain, nausea, vomiting, incoherent speech and leukocytosis (10). The case reports describe symptoms of schizophrenia such as social withdrawal and catatonia (5). Other cases described in the literature present affective symptoms such as emotional lability, depression, anhedonia, insomnia, psychomotor slowness or agitation, and grandiose delusions (3, 11). Conduct disorder with disruptive behavior, encopresis and hyperactivity have also been reported (11). Panconesi and Mantellasi describe anxiety states and a dominant

fear of disease (12). Hamner reports a case of obsessive compulsive disorder with porphyria (13). The neuropsychiatric symptoms that are described include seizures, confusional states and delirium (4, 14, 15). Douer et al. describe a case report of a 19 year old woman suffering from an acute attack of AIP, who was disoriented and had generalized convulsive seizures. Shortly afterward she became comatose. She also suffered from abdominal pain, hypertension and tachycardia. Her symptoms resolved after intravenous administration of high doses of propranolol (16). Atsmon and Blum describe another case of a 26 year old woman with variegate porphyria manifested by periods of mental confusion and hallucinations, as well as gastrointestinal symptoms. The symptoms subsided following several days of propranolol treatment (17, 18). Other psychiatric symptoms include abnormalities in form and content of thought, hysteria and various personality changes (4, 14, 19, 20). The same patient may manifest different psychiatric symptoms during separate attacks. Santosh and Malhotra illustrated this by describing a case of a 14 year old Indian boy who experienced symptoms of catatonia, hallucinations or hypomania over the course of separate hospitalizations (21). Suarez et al. reviewed medical histories of 1039 patients diagnosed with AIP reported in the medical literature and found that the most common psychiatric manifestations were delirium (22%), depression (8%) and psychosis (7%) (22). Forty percent of clinical cases of AIP present with mental confusion or hallucinations (23). Although psychiatric symptoms in AIP are common, cases with psychiatric symptoms as the only manifestation, as in the case we present above, are rare. Tishler et al. described a few such cases. In their psychiatric inpatient screening for AIP, a 16 year old black boy with depressive symptoms and ideas of reference but no abdominal or neurological symptoms was diagnosed with AIP. Another case which was diagnosed with AIP in the same study was that of an elderly man who had been institutionalized for 40 years with aggressive, inappropriate behavior and with periods of withdrawal and depression. Abdominal symptoms were prominent only in one out of the eight positively diagnosed subjects in this study (5). It is possible that cases with psychiatric symptoms as the only

manifestation are rare due to under diagnosis of porphyria in such patients.

It was reported that acute porphyria was more common in patients with psychiatric illness than in the general population. (1, 3-5, 21, 24, 25). Tishler et al. screened 3867 psychiatric inpatients for AIP and found a prevalence of 210 cases per 100,000 psychiatric hospital inpatients (5). This is much higher than the occurrence in the general population (1-2/100000) (2). The DSM-III diagnoses of the psychiatric patients diagnosed in this study as having AIP were atypical psychosis and schizoaffective disorder (5).

Many medications can precipitate or exacerbate attacks and therefore should be avoided. Commonly used offenders include many psychotropic medications that may cause further worsening of the symptoms in patients with undiagnosed porphyria who are hospitalized in psychiatric hospitals. Among them are barbiturates, valproic acid, carbamazepine, imipramine, nortriptyline and amphetamines. Antibiotics such as sulphonamides and erythromycin are also porphyrogenic drugs to be avoided (1). In the case presented, sulphonamides and an infection were most probably the combination which precipitated the first episode. Stress may have precipitated the second one. During hospitalization, prior to being diagnosed with AIP, the patient was treated with perphenazine and risperidone. This treatment improved his symptoms. There is little information regarding the safety of these drugs in AIP patients, although in existing reports they are described as safe and this case strengthens this assumption (26, 27).

As mentioned earlier, AIP may present with purely psychiatric symptoms, thus causing a diagnostic dilemma. It may manifest as a psychosis, and the patient may be treated erroneously for schizophrenia for many years (4). Moreover, usage of porphyrogenic drugs in such patients may result in permanent neurological and mental damage, or may even cause death (2, 4). The only way to recognize porphyria is to consider the possibility of this diagnosis, especially in patients with a recent history of possible precipitating factors, and to conduct a proper investigation with consultation of a porphyria laboratory specialist.

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