A high urinary urobilinogen / serum total bilirubin ratio reported in abdominal pain patients can indicate acute hepatic porphyria

Chengyuan Song
Qilu Hospital of Shandong University

Yuan Liu (liuyuan@qiluhospital.com)
Shandong University Qilu Hospital  https://orcid.org/0000-0003-4991-552X

Research Article

Keywords: acute hepatic porphyria, urinary urobilinogen, serum total bilirubin

Posted Date: November 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-587707/v3

License: © ① This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background: Due to its variable symptoms and nonspecific laboratory test results during routine examinations, acute hepatic porphyria (AHP) has always been a diagnostic dilemma for physicians. Misdiagnoses, missed diagnoses, and inappropriate treatments are very common. Correct diagnosis mainly depends on the detection of a high urinary porphobilinogen (PBG) level, which is not a routine test performed in the clinic and highly relies on the physician's awareness of AHP. Therefore, identifying a more convenient indicator for use during routine examinations is required to improve the diagnosis of AHP.

Results: In the present study, we retrospectively analyzed laboratory examinations in 12 AHP patients and 100 patients with abdominal pain of other causes as the control groups between 2015 and 2022. Compared with the control groups, AHP patients showed a significantly higher urinary urobilinogen level during the urinalysis (P < 0.05). However, we showed that the higher urobilinogen level was caused by a false-positive result due to a higher level of urine PBG in the AHP patients. Moreover, a remarkable increase in the urinary urobilinogen/serum total bilirubin ratio was observed in AHP patients when compared to the control groups. The area under the ROC curve of this ratio for AHP was 1.000 (95% confidence interval, 1.000–1.000, P < 0.01). A cutoff value of 3.22 for the urinary urobilinogen/serum total bilirubin ratio yielded a sensitivity of 100% and a specificity of 100% to distinguish AHP patients from the controls.

Conclusion: A reported high urinary urobilinogen level that was adjusted by the serum total bilirubin level (urinary urobilinogen/serum total bilirubin ratio) could be used as a sensitive and specific screening marker for AHP in patients with abdominal pain.

Background

Acute hepatic porphyria (AHP) is a rare but life-threatening disease. During the acute attack of AHP, abdominal pain is the most common presentation and the leading reason for the emergency visit(1). However, due to the various symptoms and nonspecific routine laboratory test results, the diagnosis of AHP has always been a significant challenge for the physicians, and a delay in diagnosis or even misdiagnosis is very common (1–3). There are four classes of AHP: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and aminolevulinic acid dehydratase deficient porphyria (ADP)(4). Since ADP is extremely rare and presenting a different laboratory results(5), we mainly focused on AIP, HCP and VP which are more common classes with elevated urinary porphobilinogen (PBG) during attack, in the present study. The examination of urinary PBG is the key test in patients with suspected AIP, HCP and VP(6). However, as an unconventional examination, the urine PBG is detected only when the physicians realize the possibility of AHP. Moreover, only several hospitals in mainland of China carried out the detection of urinary PBG which also greatly compromises the diagnosis of this rare disease(7).

The Watson-Schwartz test has been a widely used method for urinary PBG detection for more than 80 years. Ehrlich's reagent in the first step reacts with PBG and forms a red condensation product. However, PBG is not the only substance that can react with Ehrlich's reagent. Ehrlich's reagent also reacts with urobilinogen(8). As such, in the second step of Watson-Schwartz test, chloroform is added to the solution to distinguish the PBG-Ehrlich compound from the urobilinogen-Ehrlich complex. Red color in the aqueous phase of the test tube after adding chloroform illustrates the existence of the PBG-Ehrlich compound while red color in the chloroform phase proves the existence of the urobilinogen-Ehrlich complex. At present, the dipstick method is the most widely used method of urinalysis. The Ehrlich's reagent pad on the dipsticks is used for detection of urinary urobilinogen. However, it is impossible to use chloroform to distinguish the PBG-Ehrlich compound from urobilinogen-Ehrlich complex when the reaction happened on the pad. Moreover, we checked the urinary urobilinogen result of one AHP patients in our hospital and found that a positive result showed on the dipstick while a negative result showed using the Watson-Schwartz test (supplementary material). This finding proved the false-positive result of urinary urobilinogen in AHP patients.

Urobilinogen is a product of bilirubin metabolism by anaerobic bacteria in the intestine. Up to 20% of the urobilinogen produced daily are reabsorbed from the intestine and undergo enterohepatic recirculation. The majority of the reabsorbed urobilinogen is taken up by the liver and then re-excreted into bile, while a small amount is excreted in the urine and being detected as urinary urobilinogen(9). In healthy people, the urinary urobilinogen in urinalysis is negative since the amount of urobilinogen is too low to be detected. However, in certain diseases, such as hemolytic anemia, hepatic jaundice, and biliary disease, the serum bilirubin level is greatly elevated and leads to the excessive production of urobilinogen. Thus, a positive result shows in the urinalysis(10, 11). So we believed that using serum total bilirubin for calibration could help the doctors to identify the false-positive urinary urobilinogen and furthermore suspect the diagnosis of AHP.

In the present study, we analyzed the urinary urobilinogen and serum bilirubin in the AHP patients and discovered for the first time that both the urinary urobilinogen and the urinary urobilinogen/serum total bilirubin ratio were greatly increased in the AHP group compared with the control groups, indicating its potential clinical value in screening AIP, HCP and VP during the routine examination. Furthermore, the sensitivity and specificity of this ratio were assessed to evaluate the performance of the urinary urobilinogen/serum total bilirubin ratio as a convenient indicator during the acute attack of AIP, HCP and VP.

Results

Demographic and clinical characteristics of the AHP patients
Between 2015 and 2021, 12 AHP patients were admitted into our hospital. The mean age at diagnosis was 27.7 ± 6.8 years old, with a female/male ratio of 11:1. These patients had 4.8 ± 1.9 acute attacks with a maximum of eight attacks before the correct diagnosis. Abdominal pain (100%), pain in the extremities (50.0%), seizures (33.3%), and dark urine (16.7%) were common clinical presentations. During the physical examinations, tachycardia and hypertension were observed in 75.0% and 58.3% of the patients, respectively. None of the patients reported skin lesions. In seven of the patients, AHP was triggered by hormonal variations during pregnancy or the menstrual cycle. In one patient, AHP was triggered by alcohol intake. No clear causes were recorded for the remaining four patients (Table 1).

| Case | Sex  | Age | Precipitating factors | Abdominal pain | Pain in the extremities | Seizures | Dark urine | Skin lesions | Blood pressure (mmHg) | Pulse rate/min | Watson-Swartz test | Gene mutation |
|------|------|-----|-----------------------|----------------|-------------------------|----------|------------|-------------|-----------------------|--------------|-------------------|---------------|
| 1    | Female | 20  | Menstruation          | Yes            | No                      | No       | No         | No          | 149/87                 | 112          | Positive          | N/A           |
| 2    | Male   | 24  | Alcohol               | Yes            | Yes                     | Yes      | No         | No          | 107/62                 | 101          | Positive          | N/A           |
| 3    | Female | 37  | Pregnancy             | Yes            | No                      | No       | No         | No          | 146/94                 | 86           | Positive          | Yes (HMBS)    |
| 4    | Female | 28  | Pregnancy             | Yes            | Yes                     | Yes      | No         | No          | 137/80                 | 104          | Positive          | N/A           |
| 5    | Female | 32  | Menstruation          | Yes            | No                      | Yes      | No         | No          | 111/87                 | 116          | Positive          | N/A           |
| 6    | Female | 19  | Unknown               | Yes            | Yes                     | No       | Yes        | No          | 144/113                | 123          | N/A               | Yes (HMBS)    |
| 7    | Female | 23  | Menstruation          | Yes            | Yes                     | No       | No         | No          | 169/120                | 112          | Positive          | N/A           |
| 8    | Female | 35  | Menstruation          | Yes            | No                      | No       | Yes        | No          | 161/89                 | 86           | Positive          | N/A           |
| 9    | Female | 29  | Unknown               | Yes            | No                      | No       | No         | No          | 97/68                  | 122          | Positive          | N/A           |
| 10   | Female | 27  | Unknown               | Yes            | No                      | No       | No         | No          | 150/78                 | 78           | Positive          | N/A           |
| 11   | Female | 18  | Unknown               | Yes            | Yes                     | No       | No         | No          | 129/72                 | 123          | N/A               | Yes (HMBS)    |
| 12   | Female | 25  | Menstruation          | Yes            | Yes                     | Yes      | No         | No          | 129/92                 | 81           | Positive          | Yes (HMBS)    |

HMBS: Hydroxymethylbilane Synthase

Interestingly, half of the AHP patients were first diagnosed by endocrinologist during a consult for hyponatremia. For the other six cases, four were diagnosed by neurologists, and two were diagnosed by a gastroenterologist and surgeon. During their previous visits, these patients had been misdiagnosed as intestinal obstruction (83.3%), undifferentiated abdominal pain (75.0%), appendicitis (8.3%), and seizure (16.7%). Appendectomy was performed in one patient at the primary hospital and seizures happened after the surgery.

Elevated urinary urobilinogen and urinary urobilinogen/serum total bilirubin ratio was found in AHP patients

One hundred patients with abdominal pain caused by other diseases were enrolled in the control groups, and their laboratory results were compared with those of the AHP patients. During the acute attack, the AHP patients showed significantly lower hemoglobin, serum sodium, and serum chlorine, and higher urinary urobilinogen levels compared with control groups. There was no significant difference in total bilirubin levels among the groups (Table 2). However, a remarkable increase in urinary urobilinogen/serum total bilirubin ratio in AHP patients (6.19 ± 1.88 vs. 0.00 ± 0.0, P < 0.01) was observed when compared with that in the control groups (Fig. 1).
|                  | Cholecystitis and gallstones (N = 25) | Intestinal obstruction (N = 25) | Pancreatitis (N = 25) | Appendicitis (N = 25) | Acute hepatic porphyria (N = 12) |
|------------------|--------------------------------------|-------------------------------|----------------------|----------------------|----------------------------------|
| Male/female ratio| 13:12                                | 10:15                         | 13:12                | 10:15                | 1:11                             |
| Age              | 67.00 (60.50, 69.00)**                | 52.96 ± 16.04**               | 52.48 ± 15.48**      | 42.80 ± 17.97**       | 27.73 ± 6.77                     |
| Hemoglobin       | 133.64 ± 16.08*                      | 133.16 ± 18.25*              | 140.29 ± 21.35**     | 137.04 ± 20.37*       | 107.75 ± 13.79                   |
| Age              | 67.00 (60.50, 69.00)**                | 52.96 ± 16.04**               | 52.48 ± 15.48**      | 42.80 ± 17.97**       | 27.73 ± 6.77                     |
| Hemoglobin       | 133.64 ± 16.08*                      | 133.16 ± 18.25*              | 140.29 ± 21.35**     | 137.04 ± 20.37*       | 107.75 ± 13.79                   |
| ALT (range 21–72 U/L) | 37.00 (20.50, 137.00)                | 22.50 (20.00, 27.75)**        | 63.50 (33.50, 233.50) | 25.00 (20.00, 42.00)** | 41.50 (32.50, 83.00)             |
| AST (range 17–59 µmol/l) | 28.00 (23.50, 150.00)                | 26.00 (21.00, 34.00)*         | 47.00 (32.00, 199.00) | 23.00 (19.50, 33.00)*   | 43.00 (29.50, 106.60)            |
| Serum TBIL (range 3–22 µmol/l) | 16.00 (10.50, 35.50)                | 14.00 (11.00, 20.50)          | 20.00 (12.50, 32.00)  | 16.00 (10.00, 22.00)   | 13.00 (10.90, 19.50)             |
| Serum DBIL (range 0–5 µmol/l) | 0.00 (0.00, 0.00)                   | 0.00                          | 0.00                 | 0.00                 | 0.00                             |
| Serum IBIL (range 0–19 µmol/l) | 9.00 (7.00, 18.00)                  | 11.00 (7.00, 16.00)           | 13.00 (8.50, 23.50)   | 11.00 (7.00, 16.00)   | 11.38 ± 7.34                     |
| Serum amylase (range 30–110 U/L) | 69.50 (57.25, 83.00)                | 72.00 (59.00, 72.00)          | 531.00 (238.00, 1021.50)** | 75.50 ± 34.00       | 65.25 ± 27.04                    |
| Serum sodium (range 137–145 mmol/l) | 136.43 ± 3.37**                    | 135.46 ± 3.71**              | 136.25 ± 3.08**      | 137.42 ± 4.34**       | 128.17 ± 8.93                    |
| Urinary urobilinogen | 0.00 (0.00, 0.00)**                 | 0.00 (0.00, 0.00)**           | 0.00 (0.00, 0.00)**  | 0.00 (0.00, 0.00)**   | 109.55 ± 57.03                   |

ALT: alanine transaminase; AST: aspartate transaminase; DBIL: direct bilirubin; IBIL: indirect bilirubin; TBIL: total bilirubin; *P < 0.05, ** P < 0.01.

**Performance of urinary urobilinogen/serum total bilirubin ratio as an indicator for AHP**

The performance of urinary urobilinogen/serum total bilirubin ratio as an indicator for AIP, HCP and VP was assessed by generating a ROC curve (Fig. 2). Since one patient did not undergo the urinary examination, only data from eleven AHP patients were used for the ROC analysis. With the 100 samples from abdominal pain patients of other causes as the controls, the area under the ROC curve of urobilinogen/serum total bilirubin ratio for AHP was 1.000 (95% CI, 1.000–1.000, P < 0.01). When using the maximum paired sensitivity and specificity values from the ROC curve, we determined a cutoff value of 3.22 for the urinary urobilinogen/serum total bilirubin ratio in indicating AIP, HCP and VP from abdominal pain patients. The sensitivity, specificity, PPV, and NPV of the urinary urobilinogen/serum total bilirubin ratio to identify patients with AHP were 100%, 100%, 100%, and 100%, respectively.

**Discussion**

AHP is an autosomal dominant genetic disorder caused by the defect of the enzymes during heme biosynthesis pathway(15). Due to the partial deficiency of these enzymes, excess amounts of 5-aminolevulinic acid (ALA) and PBG accumulate and cause dysfunction of the autonomic system and neuropathy(16). Common presentations of AHP include abdominal pain (85–95%), constipation (48–84%), extremity pain (50–52%), nausea and vomiting (43–88%), tachycardia (28–80%), and hypertension (36–54%)(1). Bullous skin lesions may be present during an attack of VP or HCP(17). In severe cases, seizures, hallucination and respiratory distress might also present and patients could require intensive care(18). In our study, 100% of patients complained of abdominal pain, which was much higher than that reported in previous studies. This might be due to a potential missed diagnosis of AHP patients with other symptoms caused by the poor awareness of physicians in our hospital.
The key issue in AHP management is to suspect the diagnosis(19), and the elevation of urinary PBG is the main diagnostic criteria for AHP including AIP, HCP and VP (17). However, the urine PBG detection, which is not a routine examination, is only ordered and performed when AHP is suspected by physicians. In our study, we found that 50% of the patients were diagnosed by endocrinologist, which was rare in the published articles whose authors usually were from the neurology, general surgery or emergency departments. This finding highlights the importance of experienced physicians for AHP diagnosis. However, as a rare disease, awareness of AHP in China is limited(7). According to a previous investigation carried out in a tertiary hospital in China, the misdiagnosis rate of AHP was 70% in their hospital(12). Further, case reports are barely reported from secondary or communal hospitals. Thus, finding an indicator during routine examinations is needed to help physicians notice the possibility of AHP.

In the present study, we found that all the AHP patients showed a false-positive result of urinary urobilinogen which could be used as a sentive marker for AHP screening in patients with abdominal pain. However, true-positive results of urinary urobilinogen caused by the elevated serum total bilirubin were found in several of the patients with cholecystitis and gallstones. Furthermore, we found that most of the AHP patients showed normal serum bilirubin levels, consistent with the literature(12, 18, 20–22). This indicated that urinary urobilinogen combined with serum total bilirubin could be used to distinguish the false-positive result from the true-positive result. So we analyzed the urinary urobilinogen/serum total bilirubin ratio in a cohort of patients with abdominal pain including AHP and other causes. Here, for the first time, we reported the important role of the urinary urobilinogen/serum total bilirubin ratio in the screening of AIP, HCP and VP. Compared to the abdominal pain patients of other causes, the AHP patients showed a significantly higher urinary urobilinogen level and urinary urobilinogen/serum total bilirubin ratio. Via ROC curve analysis, we found that the cutoff point for AHP diagnosis was 3.22. So in patients with typical clinical symptoms such as abdominal pain, the AHP diagnosis should be considered and further investigation of urinary PBG and ALA should be carried out when the urinary urobilinogen was positive. Especially when the urinary urobilinogen/serum total bilirubin ratio was above 3.22, a very high specificity was found for AHP screening.

In certain diseases, such as hemolytic anemia and hepatic jaundice, the serum bilirubin level is greatly elevated and leads to the excessive production of urobilinogen. Thus, a true-positive result shows in the urinalysis(10, 11). And according to previous reports, sulfonamides, p-aminosalicylic acid, and drugs containing Azo dyes (nitrofurantoin, riboflavin, methylodopa) could also react with Ehrlich’s reagent(23), leading to a false-positive result. However, abdominal pain is not common in these disease and a detailed history taking and physical examination are really necessary.

The potential clinical use of the urinary urobilinogen/serum total bilirubin ratio suggests the importance of urinalysis in the diagnosis of AIP, HCP and VP. Unlike the serum total bilirubin, which is a routine examination used for differential diagnosis of abdominal pain, urinalysis is often overlooked both by patients and physicians. In fact, dark urine is very common in AHP patients and sometimes becomes the first clue for AHP patients with seizures in the intensive care unit(3, 24). However, all the urine specimens showed amber color during urinalysis, but only two patients mentioned a change of urine color in their complaints in the present study. In addition, a menstrual period is a common predisposing factor of an acute attack, but urinalysis is often avoided both by the physicians and female patients during their periods. Therefore, we strongly suggest that all patients with abdominal pain undergo urinalysis, and the urinary urobilinogen/serum total bilirubin ratio should be calculated to indicate a diagnosis of potential AIP, HCP and VP.

Our study has several limitations. Since the urinary ALA examination were not available in our hospital, it is difficult to identify the accurate class of AHP. Meanwhile, neither the urinary urobilinogen and PBG is quantitative detection, so we could not analyze the relation between these two results. Moreover, since AHP is a rare disease, we only enrolled 12 patients from one single center in this study. Due to the limited sample size and semiquantitative result of urinary urobilinogen, there might be variations in the cut-off point. Future multi-center studies with larger sample sizes are needed. And this ratio is not suitable for the hospital where the urinalysis was detected using a diazonium salt in an acid buffer.

Conclusions

In patients with abdominal pain, the urinary urobilinogen/serum total bilirubin ratio can be used as an indicator for AIP, HCP and VP. With a cutoff point of 3.22, this ratio had a specificity and sensitivity of 100% and 100%, respectively. This finding may greatly improve the diagnosis of AIP, HCP and VP. When the urinary urobilinogen is positive, especially when the ratio is higher than 3.22, further investigation of urinary PBG, ALA or a genetic test is recommended.

Methods

Study design and participants

We reviewed patients with AHP who were admitted to Qilu Hospital, Shandong University between 2015 and 2021. Patients were diagnosed as AHP (including AIP, CHP and VP) if they met the following diagnostic criteria(7), (i) acute attack symptoms: severe abdominal pain in the absence of significant abdominal tenderness and neuropathic symptoms such as seizures; and (ii) a positive result for urinary PBG (N = 10) or a genotype with a mutation in the hydroxymethylbilane synthase, protoporphyrinogen oxidase and coproporphyrinogen oxidase genes (N = 4).

According to studies of AHP in China, the common misdiagnosis of AHP includes intestinal obstruction, pancreatitis, appendicitis, cholecystitis, and gallstones(12). We randomly enrolled 100 patients with intestinal obstruction, pancreatitis, appendicitis, and gallbladder diseases as the control group from the emergency department between January to August of 2022. The urinary PBG were tested in the control groups to exclude AHP. Patients with appendicitis (N = 25) and gallbladder diseases (N = 25) were surgically treated. Their classic symptoms and postoperative pathology results confirmed the diagnosis. The diagnosis of pancreatitis (N = 25) was established by the presence of more than two of the following criteria: (i) abdominal pain...
consistent with pancreatitis; (ii) serum amylase and/or lipase greater than three times the upper limit of normal; and/or (iii) characteristic findings from abdominal imaging (e.g., exudation around the pancreas) (13). Intestinal obstruction (N = 25) was confirmed by clinical signs and symptoms and a triad of multiple air-fluid levels, distention of small bowel loops, and the absence of gas in the colon during the abdominal imaging plain upright abdominal radiography or CT scan(14). Patients with a history of tumor, hemolytic disease, liver cirrhosis, splenomegaly, and autoimmune hemolytic anemia were excluded.

The study protocol was approved by the Medical Ethics Committee of Qilu Hospital, Shandong University, China (approval number:KL2021027). Informed consent was obtained from all the patient who participated in this study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

The medical history, physical examination, as well as blood and urinary biochemical results were collected from the Electronic Medical Records of the patients. The blood biochemical tests included hemoglobin, alanine transaminase, aspartate transaminase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, amylase, serum sodium. These tests were performed using standard hospital laboratory techniques. BC-5390CRP (Mindray Biomedical Electronics Co., Ltd, China) was used for the hemoglobin examinations. The remaining serum markers were measured using a Vitros 5600 (Ortho Clinical Diagnostics, USA). Urinary urobilinogen was carried out using Ehrlich reaction on urine test strips (CombiScreen11SYS PLUS). The strips were inserted in a fresh random urine sample for one second and then the results were compared with the color scale for urobilinogen after 30–60 seconds. There are five grades of a pink colored scale increasing in intensity with increasing of urobiligen level. The first color grade means normal, second 35umol/l, third 70umol/l, forth 140umol/l and fifth 200umol/l. Qualitative detection of urinary PBG was carried out using Watson-Schwartz test and the Ehrlich's reagent was purchased from Solarbio life sciences, China.

Statistical Analyses

All the statistical analyses were performed in SPSS (version 24.0, SPSS, Chicago, IL, USA). Normally distributed continuous data (assessed by the Shapiro-Wilk test) are presented as mean ± SD and were analyzed by the independent sample t-test. Non-normally distributed data are presented as median (percentage) and were analyzed by the Mann-Whitney U test. The diagnostic performance was measured as sensitivity, specificity, and accuracy. The cut-off for optimal clinical performance was determined by the receiver operator characteristic (ROC) curve. Results were considered significant at a P < 0.05.

Abbreviations

AHP  acute hepatic porphyria
PBG  porphobilinogen
ALA  5-aminolevulinic acid
RBC  red blood cell
ALT  alanine transaminase
AST  aspartate transaminase
TBIL  total bilirubin
DBIL  direct bilirubin
IBIL  indirect bilirubin.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of Qilu Hospital, Shandong University, China (approval number:KL2021027). Informed consent was obtained from all the patient who participated in this study. The study was conducted in accordance with the principles of the Declaration of Helsinki.
References

1. Cardenas JL, Guerrero C. Acute intermittent porphyria: general aspects with focus on pain. Current medical research and opinion. 2018;34(7):1309-15. Epub 2018/02/01.
2. Liu YP, Lien WC, Fang CC, Lai TI, Chen WJ, Wang HP. ED presentation of acute porphyria. The American journal of emergency medicine. 2005;23(2):164-7. Epub 2005/03/15.
3. Bronisch O, Stauch T, Haverkamp T, Beykirch MK, Petrides PE. Acute porphyrias: a German monocentric study of the biochemical, molecular genetic, and clinical data of 62 families. Annals of hematology. 2019;98(12):2683-91. Epub 2019/11/21.
4. Stolzel U, Doss MO, Schuppan D. Clinical Guide and Update on Porphyrias. Gastroenterology. 2019;157(2):365 – 81 e4. Epub 2019/05/16.
5. Ventura GL, Bawlani P, Bissell M, Rees DM, Stolzel DC U. et al. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. Hepatology 2020;71(5):1546–58. Epub 2019/09/13.
6. Deacon AC, Elder GH. ACP Best Practice No 165: front line tests for the investigation of suspected porphyria. Journal of clinical pathology. 2001;54(7):500-7. Epub 2001/06/29.
7. Yang J, Zhu T, Zhao Y, Yu X, Zhu H, Jiang Y, et al. Acute Intermittent Porphyria in the North of China: The Acute Attack Effect on Quality of Life and Psychological Condition. BioMed research international. 2018;2018:3216802. Epub 2018/06/05.
8. Watson CJ, Bossenmaier I, Cardinal R. Acute intermittent porphyria. Urinary porphobilinogen and other Ehrlich reactors in diagnosis. JAMA: the journal of the American Medical Association. 1961;175:1087-91. Epub 1961/03/25.
9. El-Guindi MA, El-Said HH, Hussein MH, Nassar Rel S, Sira AM. Urinary urobilinogen in biliary atresia: A missed, simple and cheap diagnostic test. Hepatology research: the official Journal of the Japan Society of Hepatology. 2016;46(2):174 – 82. Epub 2015/07/21.
10. Bennink RJ, Tulchinsky M, de Graaf W, Kadry Z, van Gulik TM. Liver function testing with nuclear medicine techniques is coming of age. Seminars in nuclear medicine. 2012;42(2):124 – 37. Epub 2012/02/02.
11. Zghieb H, Wakil C, Shaya S, Mailhac A, Al-Taki M. El Sayed M, et al. Utility of liver function tests in acute cholecystitis. Annals of hepato-biliary-pancreatic surgery. 2019;23(3):219 – 27. Epub 2019/09/11.
12. Wang Y, Chen XY, Li Y, Dong XH, Xu F. [Clinical characteristics of 50 patients with acute intermittent porphyria]. Zhonghua nei ke za zhi [Chinese journal of internal medicine]. 2019;58(7):520-4. Epub 2019/07/05.
13. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. The American journal of gastroenterology. 2013;108(9):1400-15; 16. Epub 2013/07/31.
14. Broek T, Krielen RPG Di Saverio P Coccolini S, Biffi F, Ansaloni WL L, et al. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. World journal of emergency surgery: WJES. 2018;13:24. Epub 2018/06/28.
15. Anderson KE. Acute hepatic porphyrias: Current diagnosis & management. Molecular genetics and metabolism. 2019;128(3):219 – 27. Epub 2019/07/18.
Figures

Figure 1

Comparison of urinary urobilinogen/serum total bilirubin ratio between acute hepatic porphyria patients and abdominal pain patients from other causes.

A remarkable increase in urinary urobilinogen/serum total bilirubin ratio was observed in acute hepatic porphyria patients when compared with that in the control groups (6.19 ± 1.88 vs. 0.00 ± 0.0, P < 0.01). Data are presented as mean ± SD median (percentage). An independent sample t-test was used for statistical comparisons.
Figure 2

Diagnostic performance of urinary urobilinogen/serum total bilirubin ratio for acute hepatic porphyria.

ROC curves were plotted using data from the acute hepatic porphyria patients and abdominal pain patients of other causes to assess the performance characteristics of urinary urobilinogen/serum total bilirubin ratio for acute hepatic porphyria. AUC was 1.000 with a 95% CI of 1.00–1.00. Cutoff point = 3.22

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarymaterial.docx