Letter to the Editor

Biomarkers that predict attacks of acute intermittent porphyria

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We appreciate that Dr. Bruce Wang agrees with us regarding the importance of identifying known triggers of acute attacks in acute intermittent porphyria (AIP) (1). AIP is a recurrent disease associated with severe abdominal pain, peripheral neuropathy, and central or autonomic nervous-system manifestations (2). Certain drugs and menstruation are known factors that can induce acute attacks (2). If acute-attack symptoms are not treated, they may become severe and the patient may require hospitalization (3). Although porphyria can be detected by measuring urine and stool porphyrin precursors (2), measuring porphyrin precursors does not help predict aggravation, as they can continuously increase in AIP, as demonstrated in a previous report (4). To our knowledge, no serological biomarkers for the prediction of acute attacks in AIP have been reported in post-diagnosis management. We herein discuss blood-test parameters that correlate with urinary porphyrin precursors and examine which parameters may be indicators of an acute attack. We experienced only one case; however, we obtained long-term data from the case reported here.

The patient in this case was a 20-year-old woman with acute onset AIP. She was intravenously administered 3–4 mg/kg of heme arginine acid (HA) almost monthly for 6 years because of acute attacks associated with her menstrual cycle. We previously reported the clinical course of this case (3). All 51 datasets consisting of blood and urine test results between November 7, 2014, and November 30, 2020, were analyzed in a retrospective study. As HA was administered for acute attacks, post-administration data were not included to avoid the direct effects of HA. The datasets were divided into three groups according to the clinical state during sampling: stable (asymptomatic, which is synonymous with non-attack), mild acute attack (abdominal distension and constipation), and severe acute attack (pain, tachycardia, hypertension, and seizures). Datasets were analyzed for stable periods and before HA administration in mild and severe acute attacks. The measured parameters were urinary delta-aminolevulinic acid (U-δALA) [normal value <3 mg/g creatine (Cr)], urinary porphobilinogen (U-PBG) (normal value <2 mg/g Cr), complete blood cell count, serum blood urea nitrogen (BUN), Cr, uric acid (UA), total bilirubin (Tbil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase, γ-glutamyl transpeptidase, sodium (Na), potassium (K), chloride (Cl), total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and ferritin. Pearson's correlation coefficients were calculated for the above data. The Tukey-Kramer method was used to compare whether the parameters that correlated with porphyrin precursors were significantly different in the stable, mild acute-attack, and severe acute-attack groups. Statistical analyses were performed using SPSS (ver. 26; IBM, Armonk, NY, USA).

U-δALA was correlated with U-PBG ($P<0.001$, $|r|=0.723$), Tbil ($P=0.014$, $|r|=0.341$), and serum Na ($P<0.001$, $|r|=0.492$) [*Figure 1A(i,ii,iii)*]. U-PBG was correlated with UA ($P=0.005$, $|r|=0.406$) and serum Na ($P=0.033$, $|r|=0.299$) [*Figure 1A(iv,v)*]. A correlation was also found between U-δALA and TG (triglyceride) ($P=0.033$, $|r|=0.315$) and U-PBG and LDL ($P=0.030$, $|r|=0.474$), but the postprandial blood tests showed mixed results. There was no correlation between other parameters and urinary porphyrin precursors. Urinary porphyrin precursors did not necessarily show clinical symptoms

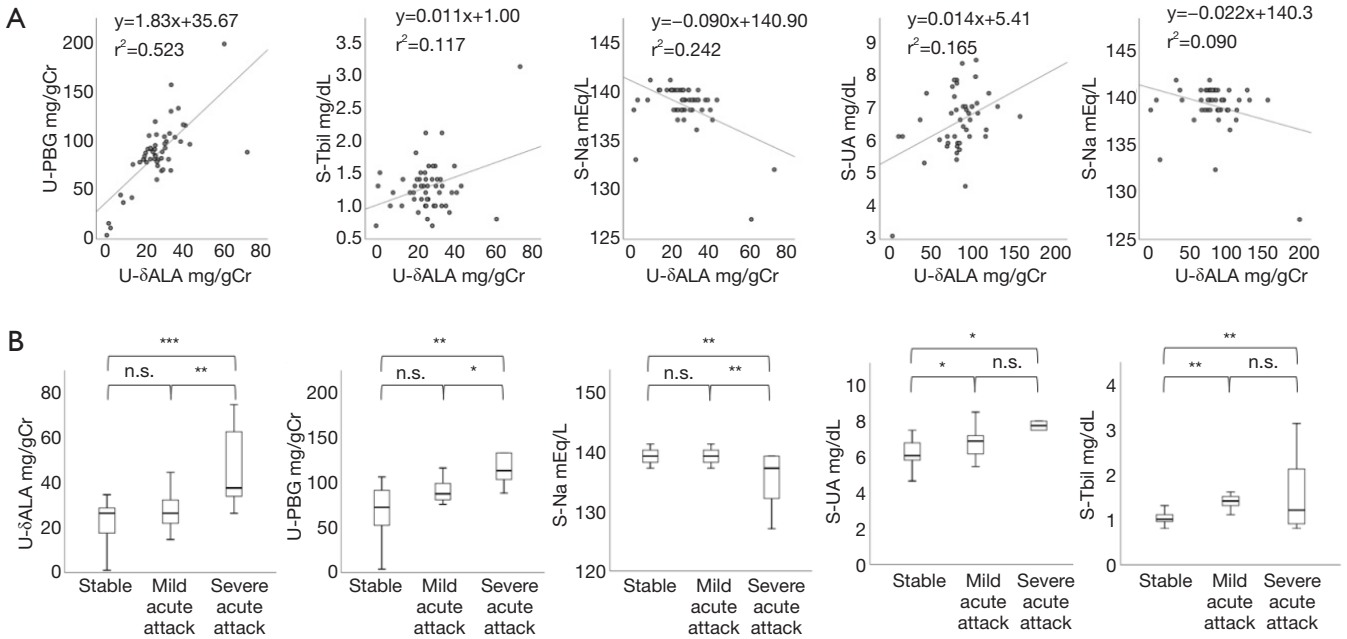

Figure 1 Blood parameters correlated with porphyrin precursors and comparison of data according to clinical state. (A) Statistical comparison using Pearson's correlation coefficient of: (i) U-δALA and U-PBG (P<0.001, |r|=0.723); (ii) U-δALA and S-Tbil (P=0.014, |r|=0.341); (iii) U-δALA and S-Na (P<0.001, |r|=0.492); and (iv) U-PBG and S-UA (P=0.005, |r|=0.406), (v) U-PBG and S-Na (P=0.033, |r|=0.299). U-δALA, urinary delta-aminolevulinic acid; U-PBG, urinary porphobilinogen; S-Tbil, serum total bilirubin; S-Na, serum sodium; S-UA, serum uric acid. (B) Statistical comparison using the Tukey-Kramer method of clinical state of: (i) U-δALA, (ii) U-PBG, (iii) S-Na, (iv) S-UA, and (v) S-Tbil. (i) n=16, stable; n=29, mild acute attack; n=6, severe acute attack; $F_{2, 48}$=9.537, P<0.001; stable *vs.* mild acute attack, P=0.448; mild acute attack *vs.* severe acute attack, P=0.001; stable *vs.* severe acute attack, P<0.001. (ii) n=16, stable; n=29, mild acute attack; n=6, severe acute attack; $F_{2, 48}$=8.178, P=0.001; stable *vs.* mild acute attack, P =0.110; mild acute attack *vs.* severe acute attack, P=0.017; stable *vs.* severe acute attack, P=0.001. (iii) n=16, stable; n=29, mild acute attack; n=6, severe acute attack; $F_{2, 48}$=8.947, P<0.001; stable *vs.* mild acute attack, P=0.942; mild acute attack *vs.* severe acute attack, P=0.001; stable *vs.* severe acute attack, P=0.001. (iv) n=15, stable; n=29, mild acute attack; n=2, severe acute attack; $F_{2, 43}$=5.640, P=0.007; stable *vs.* mild acute attack, P=0.019; mild acute attack *vs.* severe acute attack, P=0.359; stable *vs.* severe acute attack, P=0.039. (v) n=16, stable; n=29, mild acute attack; n=6, severe acute attack; $F_{2, 48}$=9.187, P<0.001; stable *vs.* mild acute attack, P=0.001; mild acute attack *vs.* severe acute attack, P=0.596; stable *vs.* severe acute attack, P=0.004. U-δALA, urinary delta-aminolevulinic acid; U-PBG, urinary porphobilinogen; S-Na, serum sodium; S-UA, serum uric acid; S-Tbil, serum total bilirubin; n.s., not significant. (*P<0.05, **P<0.005, ***P<0.001).

even if the levels exceeded the normal range, but urinary porphyrin precursor levels significantly increased during severe acute attacks [*Figure 1B(i,ii)*]. Na showed significant decrease during severe acute attacks but did not show any significant difference during mild acute attacks compared to the stable-period values [*Figure 1B(iii)*]. UA and Tbil showed significant differences between stable and mild acute attacks, but not between mild acute and severe acute attacks [*Figure 1B(iv,v)*]. The total dose of HA was 11,275 mg over 2,189 days, but no increase in ferritin was observed (n=35, mean 91.5±36.7 ng/mL). Most samples were collected 5 days before and after ovulation.

It has been reported that clinical symptoms do not always appear when the urinary porphyrin precursor level exceeds the normal value (4,5); however, in our study U-δALA and U-PBG increased as the severity of the attacks increased. Although no previous reports have shown that Tbil and UA increase during an attack, we found that elevated Tbil and UA could help predict mild acute attacks. The correlation between UA levels and renal function and between Tbil and liver damage remained unclear in our dataset. We previously proposed that systemic vascular spasm due to deficiency of nitric oxide synthase occurs in porphyria (3), but it was difficult to prove this etiology. If mild ischemia

occurs in remission, blood tests may not show liver damage with elevated AST or ALT levels or renal dysfunction with elevated BUN or Cr levels.

In our dataset, the Na level significantly decreased during severe acute attacks, but we consider this to be inevitable because the inappropriate secretion of antidiuretic hormone is known to be complicated when porphyria becomes severe with acute attacks (6). Na is a predictor for severe acute attacks but was not a predictor for mild acute attacks in our dataset. Although the use of high-dose HA is known to be a risk factor for iron overload (7), we observed no obvious adverse events. Further, mild acute attacks remained in remission with HA (3 mg/kg/day). A limitation of the study is that the data analyzed between groups were unequal, as most consultations occurred during the stable or mild acute-attack periods. It may be possible to predict mild acute attacks using Tbil and UA. The mechanism of bilirubin and UA level elevation may involve insufficient synthesis of heme promoting the destruction of erythrocytes in the reticuloendothelial system, resulting in an increase in bilirubin and UA levels. There are a few reported cases of AIP with recurrent severe acute attacks; however more data are required in the future for further insight. Our report shows that an acute attack of AIP can potentially be predicted with a simple blood test.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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