Response to Porphyria: The Neglected Diagnosis

To the Editor:

In a recent issue you published an editorial, *Porphyria: The Neglected Diagnosis* [1].

As the article emphasized, porphyria (of all types) is commonly overlooked and too often remains undiagnosed or is diagnosed after a long delay. The article on this topic is important as it enlightens and raises awareness of these neglected disorders, which can be life threatening.

However, we would like to add some important remarks to this editorial and the accompanying article [2]:

1. As the author presented, the only route to a confirmed diagnosis of an acute attack is a routine quantitative porphobilinogen test [3]. In Israel, this test is conducted by the National Service for the Biochemical Diagnoses of Porphyrias, which is the only certified laboratory dedicated to porphyria diagnosis in the country. It is affiliated with a dedicated porphyria clinic. However, while the editorial claims that this test has a "turnover time of 4 to 10 days" this is not the case in Israel. An urgent test that leaves any hospital located in Israel will arrive on the same day, and with a simple telephone call to the laboratory stating that the test is urgent, the specimen will be examined the same day or by the next morning at the latest.

2. The method that the editorial suggests, "exposing the urine to sunlight… can attribute to rapid diagnosis," is dangerous advice. Since this test is far from being sensitive or specific, it may lead to either falsely ruling out this life-threatening disease or detecting a false positive result. In any case, it cannot be trusted, and treatment should not rely on this test [3].

   When an acute attack is highly suspected and a rapid porphobilinogen result is not available, a urine sample should be obtained for future evaluation while treatment should be initiated regardless of urine color change in the sun [4,5].

   Of importance, heme treatment should be restricted to severe neurovisceral crises since it could have serious adverse events and has been suggested to increase recurrent attacks [5].

3. The article presented a seemingly case of acute intermittent porphyria. Even when elevated urinary porphobilinogen is found; the differential diagnosis includes varigate porphyria or hereditary coproporphyria, which have a similar clinical course as an acute attack but different biochemical markers. Further tests of stool and blood samples could diagnose the accurate type of porphyria [3]. Accurate diagnosis is important for further genetic analysis and for the diagnosis of silent carriers among family members in order to guide them accordingly [4,5].

We appreciate the authors' efforts to raise the awareness of porphyria, and hope these remarks will add to the readers' knowledge and awareness.

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Response to Porphyria: The Neglected Diagnosis

Response to the letter written by Yonatan Edel, Sharon Cohen, and Rivka Mamet

To the Editor:

We recently published an editorial in the *Israel Medical Association Journal* (*IMAJ*) titled *Porphyria: The Neglected Diagnosis* [1], in which we emphasized that porphyria is a neglected diagnosis, even among experienced physicians. We focused on the diagnosis of acute intermittent porphyria (AIP).

In this issue of *IMAJ*, Edel, Cohen, and Mamet clarified in their response and included important comments responding to our editorial.

1. As presented in the original editorial, the only way, currently, for a confirmed diagnosis of an acute attack is to perform a routine quantitative porphobilinogen test [1]. Edel, Cohen, and Mamet clarified that this test is conducted by the National Service for the Biochemical Diagnoses of Porphyrias, which is the only certified dedicated porphyria lab in Israel, and which is affiliated with a dedicated porphyria clinic. The group emphasized that in urgent cases, the test can be completed the same day, or at the latest by the next morning. Actually, this clarification is very important because physicians can use this service for immediate diagnosis of porphyria. Again, a strong clinical suspicion is needed for early diagnosis.

2. Edel et al. referred to exposing the urine to sunlight, which can help in diagnosis of porphyria as "dangerous advice."

   We clarify here that our editorial discussed a case presented by Khoury and colleagues [2], in the April 2019 issue of *IMAJ*. They described a typical patient with AIP. The young patient presented with severe epigastric abdominal pain and later developed severe hyponatremia. The clinical presentation of epigastric pain, hyponatremia, and

gastroparesis in combination with high clinical suspicion and knowledge of the associated manifestations enabled the clinical staff to make the diagnosis rapidly [3]. The urine was exposed to the sun light, and its color changed from light yellow to dark orange color. This change in urine color contributed to the diagnosis of AIP. Subsequently, the diagnosis of porphyria was confirmed by the presence of porphobilinogen in the urine.

I fully agree with Edel et al. that the urine color-change test is not sensitive or specific.

The urine test can only contribute to the suspected diagnosis of porphyria and the diagnosis is not conclusive. This test is surely an important test in some countries where the specific tests cannot be performed within a reasonable time period.

3. As mentioned before, our editorial discussed a case presented by Khoury and colleagues [2], in the April 219 issue, which described a patient with AIP. We agree that the differential diagnosis includes varigate porphyria or hereditary coproporphyria, which have a similar clinical course of an acute attack but different biochemical markers. Further tests in stool and blood could diagnose the accurate type of porphyria [3].

We appreciate the response to our editorial, and to these important comments and we are sure that this discussion adds a lot to the knowledge and awareness of porphyria.

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Capsule

Tackling cystic fibrosis in the womb

Cystic fibrosis (CF) is a multiorgan disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). Abnormalities in the lungs, pancreas, and gastrointestinal tract develop even before birth. **Sun** et al. reasoned that early intervention using the approved drug VX-770 (ivacaftor), a CFTR modulator, could prevent the development of such abnormalities. They tested the effect of in utero and early postnatal VX-770 administration in a ferret model of CF. Organ pathologies were partially prevented in treated ferrets, suggesting that prenatal treatment might increase the efficacy of CFTR-correcting therapies.

Sci Transl Med 2019; 11: eaau7531

Eitan Israeli

Capsule

Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer

Association studies have linked microbiome alterations with many human diseases. However, they have not always reported consistent results, thereby necessitating cross-study comparisons. **Wirbel's** group, in a meta-analysis of eight geographically and technically diverse fecal shotgun metagenomic studies of colorectal cancer (CRC, n=768), identified a core set of 29 species significantly enriched in CRC metagenomes (false discovery rate (FDR) $< 1 \times 10^{-5}$). CRC signatures derived from single studies maintained their accuracy in other studies. By focusing on multiple studies, the authors improved detection accuracy and disease specificity for CRC. Functional analysis of CRC metagenomes revealed enriched protein and mucin catabolism genes and depleted carbohydrate degradation genes. Moreover, they inferred elevated production of secondary bile acids from CRC metagenomes, suggesting a metabolic link between cancer-associated gut microbes and a fat- and meat-rich diet. Through extensive validations, this meta-analysis firmly establishes globally generalizable, predictive taxonomic, and functional microbiome CRC signatures as a basis for future diagnostics.

Nature Med 2019; 25: 679

Eitan Israeli

"The mere imparting of information is not education"

Carter G. Woodson (1875–1950), American historian known as the Father of Black History