

Medical Treatment Guidelines

Washington State Department of Labor and Industries

Collaborative guidelines on the diagnosis of porphyria and related conditions

Prepared by

**The Washington State Department of Labor and Industries
and
The Washington State Medical Association's
Committee on Industrial Insurance and Rehabilitation**

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Purpose and development of these guidelines

The purpose of these guidelines is to provide information for treating physicians and independent medical examiners to use in evaluating patients with possible exposure-related porphyria, and to provide a foundation for developing Department medical policy.

The focus of these guidelines is on the phase of the medical evaluation where a decision must be made whether to proceed with an extensive work-up to reach a definitive diagnosis, or to conclude that results of a preliminary evaluation make a diagnosis of porphyria unlikely (see Section III). It is beyond the scope of these guidelines to provide detailed algorithms for reaching a conclusive diagnosis.

These guidelines were developed with the input and approval of numerous nationally and internationally recognized experts on porphyria. Input was also incorporated from many other individuals, including physicians representing a wide variety of specialties and non-physicians with an interest in this topic.

The scientific basis for these guidelines, along with additional information about their development, can be found in a review document on porphyria prepared by the Office of the Medical Director of the Washington State Department of Labor and Industries. These guidelines may be revised as new scientific information becomes available.

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General information

Porphyrias are metabolic disorders in which the clinical manifestations are attributable to decreased activity of a specific enzyme(s) in the heme synthesis pathway, associated with characteristic patterns of overproduction of specific heme precursors and resultant accumulation in certain tissues. Each enzyme deficiency results in a predictable accumulation of the preceding heme precursor(s), and overall production of heme is generally preserved. Porphyrias, when clinically active, and in some cases even when latent or in clinical remission, are characterized by high levels of heme precursors in blood, urine, and/or stool. Most types of porphyria are inherited conditions; however, one type of porphyria, porphyria cutanea tarda, is known to occur in acquired or inherited manner.

Many of the tests used to diagnose the porphyrias are nonspecific and are abnormal in many circumstances other than the porphyrias. Porphyrinuria, i.e., increased urine porphyrins, can be caused by porphyrias, by a number of other medical conditions, and by a variety of exogenous factors such as alcohol and certain drugs and chemicals that disturb heme synthesis or stress heme-dependent metabolism. The term "secondary porphyrinuria" is commonly used in reference to the porphyrinuria occurring with conditions and factors lacking a primary enzyme defect in heme synthesis. It usually involves mild or moderate coproporphyrinuria, with no or little excess uroporphyrin in urine, and is also often called "coproporphyrinuria" or "secondary coproporphyrinuria."

In individuals who are genetically predisposed to developing an acute or cutaneous porphyria, manifestations of porphyria can be *triggered* by a variety of exogenous factors including alcohol, certain therapeutic drugs and chemicals, infections, dietary factors and sun exposure, as well as by certain medical conditions and endogenous factors such as menstruation and administered steroid hormones. Exogenous factors can also *cause* changes in the heme synthesis pathway, even in the absence of genetic predisposition; in some cases, these acquired changes have been reported to cause porphyria cutanea tarda.

Lead absorption, both acute and chronic, is well documented to affect heme synthesis. Lead causes accumulation of protoporphyrin in erythrocytes and large increases of ALA and coproporphyrin in urine. Lead inhibits ALA dehydratase, and also appears to interfere with the function of two other heme synthesis enzymes. Lead intoxication is generally classified as a secondary porphyrinuria rather than as an acquired porphyria, although it does have clinical and biochemical similarities with acute porphyrias.

A number of chemicals, primarily halogenated hydrocarbons and metals, are known to be "porphyrogenic" (i.e., capable of inducing changes in heme synthesis, with subsequent overproduction and excessive excretion of heme precursors) in experimental animals, generally with doses much greater than the range of human experience. In humans, with the noteworthy exceptions of porphyria caused by hexachlorobenzene and the "porphyrinuria" caused by lead, reports of porphyria or porphyrinuria attributable to chemical exposures have been infrequent. It must be acknowledged, however, that there has been only limited systematic study of the subject in humans. The reported findings have generally been linked to chronic industrial exposures, industrial accidents, or environmental exposures that were much higher than normally encountered.

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Diagnosis

The most important first step toward diagnosing or ruling out porphyria in a symptomatic patient is for the physician to maintain a high index of suspicion for a possible diagnosis of porphyria, whether symptoms are "classic" for a porphyria or are vague or unexplained. The conclusive diagnosis of a porphyria should be based on a systematic approach incorporating medical history, physical examination, and biochemical data, including genetic evaluation if necessary. Certain symptom patterns, physical findings, and elements of the exposure history may raise the degree of suspicion for porphyria; however, the lack of supporting information from these sources cannot exclude a diagnosis of porphyria. Therefore, the systematic approach to evaluating a symptomatic patient with suspected porphyria should begin with laboratory evaluation.

In a person with symptoms from a porphyria, the level of the most excessively excreted heme precursor is typically at least several-fold greater than the upper limit of values found in normal individuals.

A. Minimum ("threshold") criteria

Physicians must sometimes decide whether an extensive work-up for porphyria is indicated. In order to assist clinicians in this decision, the following threshold criteria are recommended:

In a patient who is currently or recently symptomatic and who is suspected to have a porphyria, it is not probable that the patient's symptoms are attributable to a porphyria of any type unless a measurement on at least one of the following tests is greater than twice the upper limit of normal:

- **urine porphobilinogen (PBG)**
- **urine uroporphyrin**
- **fecal coproporphyrin.**
- **blood total porphyrins.**
- **urine coproporphyrin.**

B. Caveats

- 1. Reference range:** Because a reference range may be unique to the assay method and the individual laboratory performing the test, test results should be interpreted relative to the laboratory-specific reference range and/or, if sufficient general clinical experience exists, against accepted absolute reference standards.
- 2. Blood lead level:** A blood lead level should be checked to determine the possibility of lead intoxication if lead exposure is suspected, if excretion of coproporphyrin or ALA is increased, or if blood porphyrins (e.g., blood zinc protoporphyrin [ZPP]) are increased.
- 3. Repeat testing and factors affecting test results:** Laboratory test results, in general, can be compromised by a variety of factors including specimen integrity, analytical quality, limitations of analytical methods, and the applicability and specificity of reference ranges or "control" data. Issues of specimen integrity may be particularly relevant when specimens are collected and processed at one site, and then transported to a geographically distant reference laboratory.

Because of these risks, an abnormal test result generally should be confirmed by analysis of a second specimen before the test result is used to finalize a diagnostic conclusion. The need to repeat a test, of course, must be tempered by the degree of support for a

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diagnosis from other clinical and laboratory data, and by the feasibility of repeating the test (i.e., the appropriate clinical circumstances should still be present).

- 4. Enzyme measurements:** If a person is currently or recently symptomatic and is found to have reduced activity of a specific heme synthesis enzyme, but laboratory testing does not also reveal overproduction and excessive excretion of heme precursors in a pattern and levels consistent with the porphyria specific to that enzyme, then the reduction in measured enzyme activity has no probable causative relationship to the person's symptoms.
- 5. Additional testing:** Satisfaction of these "twice the upper limit of normal" criteria *does not necessarily establish* a diagnosis of porphyria. Depending on the degree and pattern of abnormalities on these tests, additional testing may be necessary to establish or exclude a diagnosis of porphyria. It is possible that an individual could have an abnormal heme precursor measurement with this degree of abnormality (i.e., twice upper normal) as a consequence of something other than porphyria (or lead intoxication). Other medical conditions can cause "secondary" porphyrinuria of this magnitude. Blood porphyrins can also be increased by this magnitude in conditions other than porphyria: for example, iron deficiency commonly produces an increase in blood zinc protoporphyrin (ZPP).
- 6. Timing of specimen collection:** Conversely, failure to satisfy these "twice the upper limit of normal" criteria *does not necessarily exclude* a diagnosis of porphyria. Heme precursor measurements in the range of one to two times the upper normal value should not be interpreted as "normal," but rather as *indeterminate or non-diagnostic*. When a patient with suspected porphyria is not currently or recently symptomatic, the levels of heme precursor excretion are generally lower and can even normalize with time. If a patient's last symptoms occurred remotely in time relative to specimen collection, it may be necessary to repeat the tests during or as soon as possible after future symptoms.
- 7. "Secondary porphyrinuria":** Porphyrinuria sometimes secondarily reflects the presence of a medical condition or exogenous factor that disturbs heme synthesis or stresses heme-dependent metabolism but produces symptoms through a separate mechanism. With the noteworthy exception of lead poisoning, the porphyrin excess in "secondary porphyrinuria" has no recognized, clinically detectable consequences of its own; symptoms associated with secondary porphyrinuria (other than lead poisoning) are attributed by most experts to the condition or agent causing the porphyrinuria, or to an unrelated cause, and not to a disturbance in heme synthesis. Although the porphyrinuria itself may be benign, the associated medical condition may be far from benign.

Medical conditions that appear to have only secondary effects on the heme synthesis pathway are appropriately evaluated with attention focused on the primary condition. Similarly, when chemical exposures are suspected as the cause of a patient's symptoms or medical condition, the exposure relationship can be characterized more specifically by assessment of the exposure situation or by quantification of the suspected chemical (or its metabolite) in blood or urine, than by measurement of heme precursors.