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Editorial

Porphyria and implication of molecular diagnosis

The first issue of the journal carried an article on Porphyria Cutanea Tarda (PCT) [1]. This issue has a letter by Vieira in reference to the article [2]. Vieira from Brazil has suggested an alternative diagnosis to the described case of PCT by Patil et al. [1,2]. It is interesting to note what Patil et al. have described to be a case of PCT (the most common porphyria), is essentially a case of Hepatoerythopoietic Porphyria (HEP). HEP is an extremely rare form of cutaneous porphyria [3].

Porphyria is a disorder of heme biosynthesis. There are eight enzymes involved in heme biosynthesis; correspondingly, there are eight genetically distinct porphyrias caused by the deficiency/deficient activity of the respective enzymes. Balwani and Desnick (2012) have described a relatively simple classification of porphyrias as: a) 4 acute hepatic, b) 1 hepatic cutaneous, and c) 3 erythropoietic cutaneous types [4]. The classification aids in remembering the predominant tissue where the heme metabolites accumulate and the associated symptomatology. The porphyrias manifest with varied and vague symptoms. Acute hepatic porphyrias typically present with intermittent neurologic attacks, commonly abdominal pain. The hepatic-cutaneous porphyrias present with photosensitive dermatitis and its sequelae. The erythrocutaneous porphyrias are characterized by photosensitive dermatitis and hemolytic anemia. Porphyrias are rare disorders; the prevalence of the most common one, PCT, is reported as 1 in 10,000. Indeed, a high degree of suspicion is required to suspect and subsequently confirm a case of porphyria [5].

Traditionally, urinary, plasma, fecal and/or erythrocyte 'porphyrin profile' and enzyme activity level is performed to screen/confirm the diagnosis of porphyria. Molecular pathology (genetic diagnosis) of porphyrias is a significant advancement. Molecular diagnosis is applicable when a known mutation, recurrently associated with the disease is detected. For novel mutations, a correlation with tissue 'porphyrin profile' and level of enzyme activity is desirable. This diagnostic detail is an important consideration, as genetic heterogeneity has been noted with porphyrias. Greater than 375 and 105 mutations have been documented till date, in Acute Intermittent Porphyria (AIP) and PCT, respectively [6]. Another significant application of genetic diagnosis is for prenatal diagnosis. In 2002, Ged et al. provided the first description of prenatal exclusion of HEP in a family [7]. HEP is a type of hepato-cutaneous porphyria, with severe deficiency of uroporphyrinogen decarboxylase (UROD) enzyme. It results from inheritance of two mutated alleles of UROD gene from asymptomatic carrier parents. HEP typically manifests below 2 years of age and is a severe mutilating disease [8]. The ability to offer a prenatal diagnosis in such families is extremely satisfying.

As molecular diagnosis of porphyria becomes increasingly feasible, an understanding of genetics of porphyrias is the need of the hour. This is the observation of Vieira from Brazil as well, while suggesting the alternative diagnosis of HEP for the described case of PCT by Patil et al. [1,2]. PCT, as well as HEP are caused by deficiency of uroporphyrinogen decarboxylase (UROD) enzyme. PCT, as the name 'tarda' implies, typically presents late, in 4th or 5th decade of life. Three types are described. Familial PCT (type II) is caused by heterozygous mutation of UROD gene; the level of enzyme activity is reduced to ~50% of normal. During a symptomatic period, the levels are further reduced to less than 20%. On the other hand, HEP results from a biallelic UROD gene mutation. Both the alleles/copies of the gene are mutated, leading to profound deficiency of enzyme and an earlier presentation. In the case described by Patil et al. the symptoms begin at the age of two years and a homozygous mutation of the UROD gene was detected. Hence it's a case of HEP rather than PCT, as clarified by Vieira [2].

Though porphyrias are genetic disorders, environmental factors play a role in precipitating acute attacks. A useful resource for the list of unsafe and safe drugs for patients with the acute hepatic porphyrias is available at the Drug Database for Acute Porphyrias (www.drugs-porphyria.com). Similarly, several susceptibility factors are known for PCT. Avoiding incriminated precipitating factors, such as alcohol, estrogens and iron supplements is recommended [4].

Treatment strategies for porphyrias vary from simple avoidance of sun exposure to as demanding as liver and bone marrow transplantation. A lot comes under the purview of a hematologist, including hematin infusions, phlebotomies and iron chelation. Research and experimental studies are being pursued to manage porphyria in novel ways, including recombinant enzyme (Porphozym for AIP), chaperones and/or protease inhibitor to rescue enzymes [9,10]. Ultimately, gene therapy remains the final promise to provide a cure. Recently, a favorable, though heterogeneous impact in a phase I gene therapy trial for AIP was observed; hematin treatment could be stopped in 2 of 8 patients [11]. Though the results of recent trials appear to be modest, it is optimistic, as "Big things have small beginnings".

Indeed, porphyrias have a varied presentation. An accurate diagnosis necessitates a correlation of the clinical presentation, tissue 'porphyrin profile', level of enzyme activity, besides molecular diagnosis.

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Conflict of interest

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