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WHEN SIMPLES WORKS: THE IMPACT OF QUALITATIVE TESTING ON THE DIAGNOSIS OF ACUTE INTERMITTENT PORPHYRIA IN THE STATE OF PIAUÍ

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ABSTRACT

Rare diseases, affecting an estimated 13 million Brazilians, face significant challenges in diagnosis and treatment due to a lack of infrastructure and specialized knowledge. This study describes the implementation and standardization of the qualitative porphobilinogen test (PBG) at the Laboratory of Immunogenetics and Molecular Biology of the Federal University of Piauí (LIB-UFPI), aiming at the diagnosis of Acute Intermittent Porphyria (IAP). The standardization of the Ehrlich test allowed the provision of an affordable diagnostic tool

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in a region with limited resources. To strengthen the health network, actions were carried out to organize and disseminate information about IAP among local health professionals. The dissemination of information was accompanied by the implementation of an efficient logistical flow, including collection, transportation, and analysis of samples in a timely manner, which made it possible to carry out early interventions. In five months, the test was responsible for the diagnosis of six patients with IAP, allowing the reduction of the patients' therapeutic itinerary. In addition, the negative results in other patients with similar symptoms directed the investigation to alternative etiologies, contributing to more accurate diagnoses. The impacts of this initiative include reducing the diagnostic time, expanding access to appropriate treatment, and strengthening the National Policy for Comprehensive Care for People with Rare Diseases in the state of Piauí. This work demonstrates how the combination of simple laboratory tools, professional training, and networking can transform the natural history of rare diseases, improving patients' quality of life and promoting significant advances in the local health system.

Keywords: Rare diseases, Porphyria, Porphobilinogen.

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INTRODUCTION

Rare diseases are characterized by affecting up to 65 people per 100,000 individuals. Worldwide, it is estimated that there are 6,000 to 8,000 different types of these conditions (HAENDEL *et al.*, 2020; DE SOUSA PEREIRA *et al*., 2024). Despite their individual rarity, these diseases, together, impact approximately 300 million people globally, including approximately 13 million in Brazil (NGUENGANG WAKAP *et al.*, 2020; FERREIRA, 2019). These conditions, for the most part, are chronic, progressive and potentially disabling, marked by clinical heterogeneity and difficulty in diagnosis, characteristics that often leave patients unassisted in the public and private health system, without access to adequate treatment or specialized genetic counseling (MARWAHA *et al.*, 2022; LLUBES-ARRIÀ *et al*, 2022). The clinical progression of these diseases, associated with the absence of early treatment, leads to irreversible sequelae, increased morbidity, and a significant reduction in quality of life. Diagnosis is one of the greatest challenges, it is estimated that patients travel, on average, between five and seven years from the onset of symptoms to the confirmation of the disease (FAYE *et al.*, 2024). This lack of timely diagnosis results not only in the progression of the disease, but also in emotional and financial distress for patients and their families, in addition to overloading the health system with symptomatic treatments and late interventions (CANNIZZO *et al.*, 2018)

The National Policy for Comprehensive Care for People with Rare Diseases (PNAIPDR) was instituted in Brazil in 2014, through Ordinance No. 199/2014 of the Ministry of Health, with the objective of promoting equity in access to diagnosis, treatment, and comprehensive care for patients with rare diseases (DA SILVA *et al.*, 2024). The policy established guidelines for the organization of care networks, prioritizing the training of professionals, the creation of specialized centers, and the strengthening of access to molecular and metabolic diagnosis. In addition, it provides access to specific medicines and therapies, often at high cost, as a way to minimize the progressive impacts of these conditions and improve the quality of life of patients and their families (LUZ *et al*., 2015). However, despite being a milestone in recognizing the needs of this group, its implementation faces significant challenges, especially in regions with insufficient health infrastructure.

The effectiveness of this policy is limited by the lack of referral centers in many regions, scarcity of trained professionals, and inequality in access to specialized diagnostic tests, which are concentrated in large urban centers. States such as Piauí and Maranhão,

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for example, which do not have reference centers for rare diseases, face even greater challenges, with patients often needing to travel to other states in search of diagnosis and treatment (PEREIRA *et al.,* 2022). In addition, the lack of adequate funding and bureaucracy in the release of orphan drugs make it difficult to provide ongoing assistance. These obstacles result in delays in diagnosis, disease progression, and significant financial and emotional impacts for patients and their families (AURELIANO *et al*., 2018). Overcoming these challenges requires a joint effort between public managers, health professionals, and research institutions to ensure the effectiveness of the policy in all Brazilian states.

It is estimated that about 80% of rare diseases have a genetic origin, caused by changes in specific genes, chromosomes, or the mitochondrial genome (LEE *et al.,* 2022). Among these, approximately 10% correspond to Inborn Errors of Metabolism (IME), a group of inherited metabolic disorders resulting from mutations in genes that encode enzymes involved in the metabolism of carbohydrates, lipids, amino acids, or nucleic acids (SAUDUBRAY *et al.,* 2018). These errors can be classified into three main categories: defects in the synthesis or degradation of complex biomolecules, defects in cellular energy production, and defects in intermediate metabolism. The absence or dysfunction of specific enzymes in these pathways leads to toxic accumulation of substances or deficiency of essential metabolites, triggering often severe clinical manifestations.

Biochemical screening and molecular diagnosis play an essential role in the early identification of IMEs, enabling therapeutic interventions before the development of irreversible complications. Early detection, through specific screenings, such as the analysis of metabolic markers in urine or blood, is essential to prevent serious sequelae, such as irreversible neurological damage, organ failure and early death (OLIVEIRA *et al*., 2001). In addition, diagnosis allows patients and their families to have access to genetic counseling, planning future pregnancies and reducing uncertainty about the prognosis of the disease.

In the context of Brazil, and especially in states with limited health infrastructure, such as Piauí, the absence of specialized centers for screening and diagnosis is a significant barrier to the effectiveness of the PNAIPDR (PEREIRA *et al*, 2023). This article presents the implementation of biochemical screenings in the Molecular Biology Laboratory of the Federal University of Piauí (LIB-UFPI), with emphasis on the qualitative detection of porphobilinogen (PBG) in urine, used in the diagnosis of Acute Intermittent Porphyria (IAP),

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discussing the impacts of this approach on changing the natural history of the disease in the state and its contribution to the implementation of PNAIPDR.

METHODOLOGY

STANDARDIZATION AND IMPLEMENTATION OF THE QUALITATIVE DETECTION TEST FOR PBG IN URINE

The study was conducted at the Laboratory of Immunogenetics and Molecular Biology of the Federal University of Piauí (LIB-UFPI), focusing on the standardization of the Ehrlich test, a qualitative technique used to detect PBG in urine, a specific marker for IAP crises. The method was based on protocols described in the scientific literature and was adapted to the available laboratory conditions (MAUZERALL *et al*, 1956).

DISSEMINATION OF INFORMATION ABOUT THE PERFORMANCE OF THE TEST

As a strategy to expand access to diagnosis, dissemination actions were carried out among health professionals in hospitals in the city of Teresina, capital of the state of Piauí. Training and workshops were promoted that addressed the relevance of diagnosing IAP, the indications of the Ehrlich test and the guidelines for sending samples to the laboratory.

RECEIPT AND ANALYSIS OF SAMPLES

Urine samples from patients suspected of having an IAP crisis were collected in sterile vials, stored under refrigeration, and transported to the LIB-UFPI within 24 hours. Laboratory staff performed initial screening to verify the integrity of the samples, proceeding to qualitative PBG detection immediately upon arrival.

DIAGNOSIS AND DATA COLLECTION

The results of the qualitative detection of PBG were recorded in standardized spreadsheets, containing information on patient identification, clinical data provided by the requesters, and the results of the examination. For each request, complementary data were collected, including age, gender, history of seizures, and possible triggering factors.

ETHICAL ASPECTS

This study was approved by the Research Ethics Committee of the Federal University of Piauí (CAAE:81637624.7.0000.5214).

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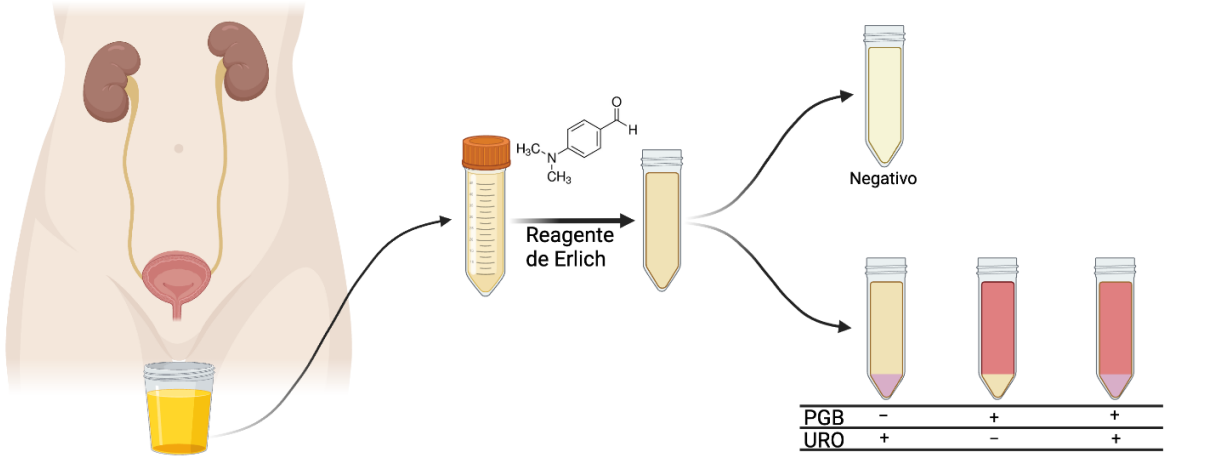
RESULTS

The Ehrlich test for the detection of PBG in urine was standardized and implemented at LIB-UFPI with the objective of filling a significant gap in the health network of the state of Piauí, where diagnostic methods for rare diseases such as IAP were non-existent. Standardization involved optimizing the preparation of the Ehrlich reagent using dimethylaminobenzaldehyde (DMAB) dissolved in concentrated hydrochloric acid, and validating the protocol to ensure reproducibility and specificity. Control urine samples, both from healthy individuals and those with a previous confirmatory diagnosis of IAP, were used to determine the sensitivity of the test, considering the formation of a characteristic color (orange-red) in the presence of PBG.

Despite its usefulness, the Ehrlich test can be susceptible to interferences, such as the reaction with urobilinogen, a compound commonly present in urine that also interacts with DMAB, generating PBG-like staining and, consequently, false-positive results. To circumvent this limitation, a confirmatory step was integrated into the protocol, using chloroform to differentiate the compounds (Watson & Schwartz, 1941). When chloroform is added to the mixture, urobilinogen is soluble in the organic phase, while PBG remains in the aqueous phase, allowing its separation and identification (Figure 01). This adaptation increases the specificity of the test, ensuring greater reliability in the results and consolidating its application in the initial diagnosis of IAP in the state of Piauí. After validation, the method was implemented at the LIB-UFPI, offering a practical and affordable alternative for diagnostic screening of IAP (Figure 01).

Figure 01: Qualitative colorimetric test for the detection of porphobilinogen in urine to aid the diagnosis of Acute Intermittent Porphyria.



PGB - Porfobilinogênio ; URO - Urobilinogênio , Reagente de Erlich - *p*-dimetilaminobenzaldeído.

Source: The author

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In order to promote the awareness and qualification of health professionals, four meetings were held involving doctors, nurses and other primary care and hospital professionals in the city of Teresina. In these meetings, the main symptoms associated with IAP were presented, such as severe abdominal pain, neuropathies and psychiatric alterations, in addition to highlighting the fragility of the diagnostic network in the state. The importance of simple and accessible qualitative tests to assist in timely diagnosis was emphasized, and the use of specific medications, already available in the Unified Health System (SUS), for crisis management was discussed. Information folders were distributed containing guidelines for diagnostic suspicion and guidelines for sending samples to the LIB-UFPI, encouraging professionals to include IAP as a hypothesis in symptomatic patients.

A flow of care was established to optimize logistics and ensure greater effectiveness in diagnosis. After collecting the urine sample in sterile vials, the professionals were instructed to store them under refrigeration and send them to the LIB-UFPI within a maximum period of 24 hours, always protected from light. Upon receiving the samples, the laboratory team performed an initial screening to verify the integrity of the material and proceeded with the execution of the qualitative PBG detection test. The results, together with the information recorded in the request form, were evaluated and returned to the requesters within 48 hours, allowing rapid therapeutic interventions when necessary (Figure 02). In addition, after receiving a positive result for IAP, patients and their families were invited to participate in a survey on the therapeutic itinerary so that, in the future, the state of Piauí can have concise data on the average time between the onset of symptoms and the diagnosis of IAP, the main challenges faced by patients and their families, in addition to allowing the monitoring of patients in the state's health network.

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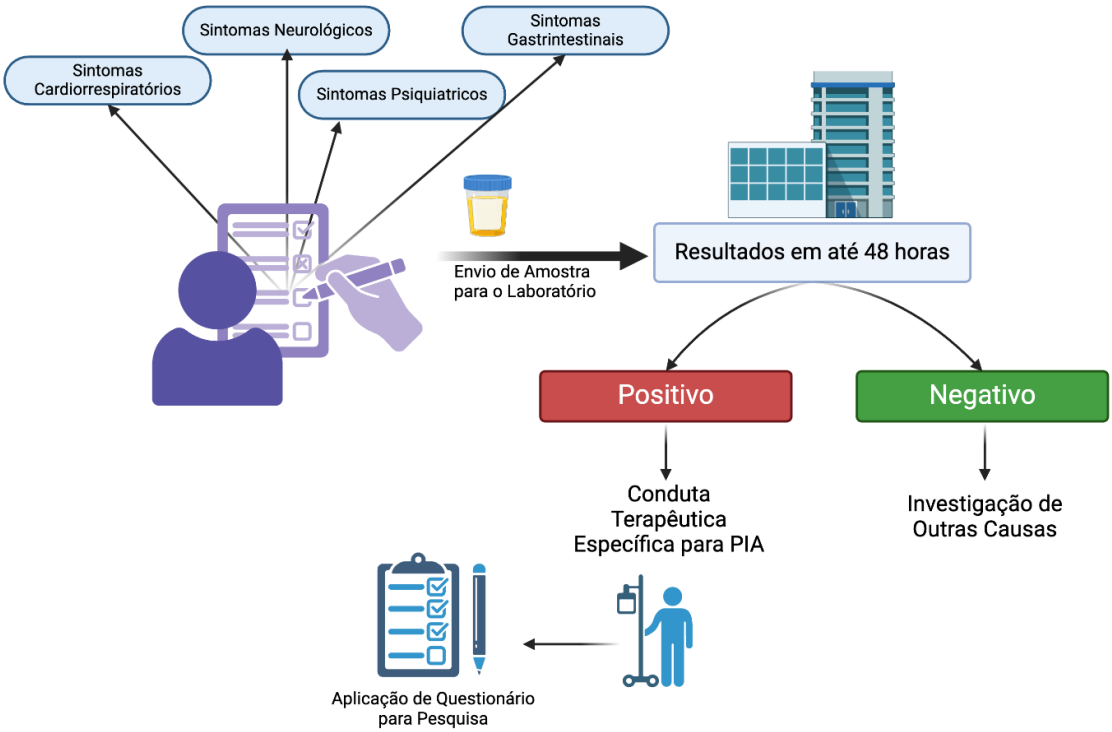
Figure 02: Proposal for a Care Network for the care of patients with Acute Intermittent Porphyria in the state of Piauí.



Source: The author

Five months after the implementation of the qualitative test for PBG detection at LIB-UFPI, the test has already been decisive in the diagnosis of six patients with IAP in the state of Piauí. These data reinforce the relevance of rapid and accessible diagnostic tools in the management of rare diseases, allowing for early and accurate interventions. Table 1 shows the clinical and demographic characteristics of the 14 patients referred for the test, of which 6 (42.8% of the sample) tested positive for PBG. All patients with a confirmed diagnosis reported typical symptoms of IAP, including bouts of severe abdominal pain, progressive muscle weakness, peripheral neuropathy, and central nervous system changes (PISCHIK *et al*., 2015). These findings highlight the positive impact of the implementation of rapid tests in the identification of rare diseases and in the reduction of diagnostic time, contributing to a better clinical outcome. A particularly relevant observation is that most patients with positive results reported having close family members with similar symptoms. This strongly suggests the presence of previously undiagnosed cases in members of the same family. In fact, one of the patients reported that a sister had already died as a result of the same symptoms presented by him, but did not have the diagnosis in life. This data reinforces the importance of family screening in the context of rare diseases, especially those of genetic origin such as IAP. The absence of diagnosis of family members before the

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implementation of the test highlights a historical gap in health care, aggravated by the scarcity of accessible diagnostic tools.

Table 01: Sociodemographic and clinical data of patients with suspected IAP treated at LIB-UFPI from June to November 2024.

Patient	Sex	Age (years)	Clinical Symptomatology	Qualitative Testing for PBG Detection	Any family members with similar symptoms?
1	M	28	Abdominal pain crises, motor paralysis, peripheral neuropathy, encephalopathy, and seizures	Positive	YES
2	M	84	- Acute flaccid weakness, axonal acute polyneuropathy	Positive	NO
3	F	40	Ascending limb paralysis and respiratory failure	Positive	YES
4	F	23	Dor abdominal, tetraparesia	Positive	YES
5	M	18	Paralysia of ascending members	Negative	NO
6	F	6	Skin symptoms when exposed to the sun	Negative	NO
7	F	43	Acute flaccid fraternity	Negative	NO
8	F	75	Polineuropatia aguda axonal	Negative	NO
9	M	70	Polineuropatia aguda axonal	Negative	NO
10	F	37	Abdominal pain crises and loss of consciousness	Negative	NO
11	F	26	Polineuropatia aguda axonal	Negative	NO
12	F	75	Polineuropatia aguda axonal	Negative	NO
13	M	45	Abdominal pain crisis associated with progressive muscle weakness	Positive	YES
14	F	39	Abdominal pain crisis associated with progressive muscle weakness	Positive	YES

Legend: M = Male; F = Female; PBG = Porphobilinogen
Source: The author

It is important to note that 8 (57.2%) of the patients referred to the LIB-UFPI with suspected IAP had a negative result for the urine PBG detection test, despite manifesting clinical symptoms such as acute axonal polyneuropathy and abdominal pain. These findings underscore that the PBG test not only aids in the diagnosis of IAP, but also plays a crucial role in its exclusion as a cause of these symptoms, directing the diagnostic investigation to other possible etiologies. This approach avoids delays in diagnosing other underlying conditions and contributes to more accurate and efficient clinical management.

The analysis of the results highlights the importance of increasing health professionals' awareness of IAP and other rare diseases, as well as integrating simple diagnostic tools, such as qualitative PBG detection, into clinical practice on a routine basis. The impact of this strategy transcends individual diagnosis, enabling family screening, genetic counseling, and early management of cases not yet identified, contributing to the effectiveness of the PNAIPDR in the state of Piauí.

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DISCUSSION

Porphyria is a group of rare metabolic diseases caused by enzymatic alterations in the heme biosynthesis pathway, which result in the accumulation of toxic metabolic precursors in body tissues and fluids (PUY *et al*., 2010; Elder *et al*., 2013). Clinically, porphyrias are classified into erythropoietic and hepatic according to the site of greatest accumulation of precursors. Among hepatic diseases, acute intermittent porphyria (IAP) stands out as the most prevalent and the only one with exclusively neurovisceral manifestations (BALWANI & DENICK, 2012). IAP is caused by a partial deficiency of the enzyme porphobilinogen deaminase (PBGD), leading to the accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), which are neurotoxic (PETRIDES, 2022). Their crises can be precipitated by factors such as cytochrome P450-inducing drugs, hormonal changes, stress, infections, and fasting, with symptoms ranging from severe abdominal pain and peripheral neuropathy to severe psychiatric changes (DESNICK *et al.,* 2001).

Accurate and timely diagnosis of IAP is essential, especially given the risk of potentially fatal acute crises, which can be triggered by medications, infections, or metabolic stress (DICKEY, 2024). Standard methods for identifying AIP involve measuring precursors such as delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) in the urine, often using techniques such as High Performance Liquid Chromatography (HPLC). However, in Brazil, less than 20% of public laboratories have the infrastructure to perform complex analyses such as HPLC and mass spectrometry (ANVISA, 2022). This limitation is even more evident in states in the North and Northeast, such as Piauí, where the shortage of specialized laboratories can result in late diagnoses or even underreporting of cases.

In addition, even when there is access to health insurance that allows urine samples to be sent to specialized laboratories, the stability of the ALA and PBG metabolites is a significant concern. Studies carried out at Cardiff and Salford centres have shThe author that porphyrins present in urine, faeces and whole blood remain stable for up to four days when stored refrigerated at 4°C and protected from light, or for up to two days at room temperature. However, the stability of PBG in urine is more sensitive, with a reduction of up to 37% in concentration after exposure to light at room temperature for one day, and up to 14% even when protected from light (WOOL *et al*, 2017). This instability can lead to false-negative results, further delaying diagnosis.

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In this context, qualitative screening tests, such as the Ehrlich reaction for the detection of PBG in urine, emerge as useful tools, especially in resource-limited settings whose large laboratories are concentrated in a single city. These tests demonstrate sensitivity greater than 85% in patients with acute symptoms of AIP (Marsden et al, 2017). The simplicity and low cost of the method make it feasible for implementation in regional services, reducing the patient's therapeutic itinerary and facilitating referral for diagnostic confirmation.

CONCLUSION

The implementation of the qualitative test for the detection of PBG in urine samples at LIB-UFPI represents an essential milestone in the diagnosis of IAP in the state of PI. This test is a crucial screening tool, allowing healthcare professionals to consider IAP as a diagnostic hypothesis in patients with suggestive symptoms, such as severe abdominal pain, peripheral neuropathy, and neuropsychiatric changes. In regions where there are no laboratories equipped to perform the quantitative measurement of ALA and PBG, the qualitative test offers an accessible and practical alternative, being especially relevant to identify suspected cases and refer them for diagnostic confirmation in centers of greater complexity.

This initiative fills a historical gap in access to the diagnosis of IAP in the state of Piauí and reinforces the principles of equity and universality of the Unified Health System (SUS). In addition to enabling early diagnosis in areas with limited infrastructure, it demonstrates how simple and accessible technologies can transform the approach to rare diseases, optimizing care and reducing diagnostic time. The experience of LIB-UFPI illustrates the positive impact of the decentralization of diagnosis and the strengthening of public health networks, highlighting the importance of training professionals to recognize rare diseases. This model has the potential to be replicated in other regions with similar challenges, promoting not only advances in the care of rare diseases, but also in the construction of public policies that prioritize equity, accessibility, and efficiency in health care.

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