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The power of the Hoesch test

El poder del test de Hoesch

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Abstract
Acute porphirias are a rare group of diseases in which the main clinical expression are abdominopsychoneurological crisis. The most typical symptom is abdominal pain.
If left untreated, acute porphyria attacks are associated with a high mortality rate (about 10%). Early diagnosis is very important. A rapid test to detect porphobilinogen (PBG) called the Hoesch test can be used for this purpose. If we have a positive test we can affirm that the clinical issues are induced by a porphyric attack. With this background, early treatment must be started with human hemin.
Our purpose is to prove the utility of the Hoesch test in the treatment period. Therefore, we made daily Hoesch tests in a porphyria crisis. We noticed that the Hoesch test remains positive without symptoms. It seems that the Hoesch test does not offer information to take the decision to stop treatment. More patients are necessary to prove this conclusion.

KEYWORDS
Acute porphyria, porphyric crisis, Hoesch test, hemine, porphobilinogen.

Resumen
Las porfirias agudas son enfermedades infrecuentes, cuya principal manifestación clínica es la crisis “abdominopsiconeurológica”. El síntoma más característico es el dolor abdominal.
La crisis porfírica sin tratamiento presenta una mortalidad del 10%. Así pues, es determinante un diagnóstico precoz en el pronóstico vital. La herramienta para realizar un diagnóstico rápido es el test de Hoesch, que detecta porfobilinógeno en la orina.
En caso de presentar un test de Hoesch positivo, podemos afirmar que la clínica del paciente se debe a una crisis porfírica. Con este diagnóstico hemos de iniciar el tratamiento con hemina.
Nuestro propósito es evaluar la utilidad del test de Hoesch como determinante en la duración del tratamiento de una crisis porfírica. En este estudio se analizó el test de Hoesch en una crisis porfírica, realizandolo a diario. Observamos que el test de Hoesch persiste positivo una vez ha desaparecido al sintomatología, por tanto no parece que pueda aportar más información a la hora de interrumpir o continuar el tratamiento. Es necesario un número mayor de pacientes para comprobar esta conclusión.

PALABRAS CLAVE
porfiria aguda, crisis porfírica, test de Hoesch, hemina, porfobilinógeno.

Contribution to scientific literature

Nowadays we know that porphyric attack could be mortal if we didn´t start the treatment. Hemine treatment is more effective than only classic treatment (glucose overdose and stop porphyrinogenic drugs), and it has demonstrated prognosis improvement of an acute attack. In present, the doubt is treatment period.

Our purpose is analyze porphyric attack with daily clinical evaluation and Hoesch test. We want to prove if Hoesch test gives information to stop or to continue treatment with hemine. We conclude that Hoesch test persists positive in spite of clinic issues dissaper. It is required a greater number of patients to make representative conclusions.

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Introduction

Porphyrias are a heterogeneous group of diseases that are caused by the toxic effects of the metabolites involved in heme group biosynthesis in various tissues. This toxic effect is caused by an increase in the concentration of heme group precursors due to enzyme deficiencies. There are mainly 7 enzymes involved in the synthesis of heme group and there can be defects in the activity of every one of them. These defects in enzymatic activity are due to mutations in the encoding genes [1].

Clinical signs and symptoms help to differentiate between porphyrias whose main manifestations are acute attacks (abdominal and neuropsychiatric) and porphyrias whose symptoms are purely cutaneous. Some types of porphyria, known as variegate porphyria and hereditary coproporphyria, can present both types of symptoms [2].

If left untreated, acute porphyria attacks are associated with a high mortality rate (about 10%) [2]; therefore, once being diagnosed the early administration of glucose solution and human hemin is essential [3,4,5]. Although it is usually recommended that heme arginate be administered for 4 days [5], it is likely that there are patients who would benefit from longer treatment. This decision should be mainly based on the absence of clinical improvement; however, other parameters, such as a semi-quantitative screening test for porphobilinogen, known as the Hoesch test, may also be taken into account when taking this decision.

Objectives

To analyze the results of the Hoesch test in a case of porphyric attack and assess its usefulness as a complementary tool to clinical signs and symptoms in taking a decision about the duration of treatment with heme arginate.

Materials and methods

A revision was done of an acute porphyria attack in a 37-year-old male who had been previously diagnosed with acute intermittent porphyria (AIP); he had a mutation in exon 6 of the porphobilinogen deaminase gene (n 267-54_61 of GAAGGGGT). The diagnosis of AIP was made 36 months before this study. The clinical signs and symptoms that he presented at that time were encephalopathy with myoclonic jerks associated with functional ileus and acute urinary retention, after having presented for years with episodes of visual hallucinations, severe behavioral disturbances and mild signs of encephalopathy, diagnosed as schizophrenia.

In recent months the patient had suffered from several decompensations attributed to various stress factors: a hypocaloric diet, poor sleep hygiene and excessive physical activity. During his last admission to hospital the intensity of the symptoms was very severe and it became necessary to prolong the administration of heme arginate for longer than is usually recommended.

During the attack that we are going to revise the patient presented with a significant tendency to fall asleep, bradypsychia, bradylalia, visual hallucinations, disorderly conduct with aggressiveness and slow-down of bowel transit. The duration of the porphyria attack was 7 days and he remained hospitalized for 19 days.

While he was hospitalized, a clinical evaluation and a Hoesch test were conducted on a daily basis from the first day of admission.

The clinical evaluation consisted of an assessment of cognitive symptoms (attention, language, presence of visual hallucinations), dysautonomia symptoms (hypertension, constipation, sweating, facial flushing) and symptoms from the peripheral nervous system (ability to stand and walk). When at least one of the symptoms or signs that had been evaluated showed a favorable response (improvement of attention or speech articulation and speech concepts, improvement in the ability to respond verbally, greater language skills, ability to understand irony, disappearance of visual hallucinations, disappearance of constipation, sweating or flushing, improved ability to stand and walk), it was considered to be evidence of clinical improvement. When any of the evaluated clinical variables worsened it was considered as evidence of clinical worsening. We talked about clinical stagnation when the clinical variables showed the same results as the previous day.

The Hoesch test was performed by mixing 1 ml of Ehrlich's reagent (2 g of dimethylaminobenzaldehyde in 20% hydrochloric acid) with 2-3 drops from a fresh sample of the patient's urine, protected from light [7]. In accordance with the usual recommendations, the test was considered to be positive when the Ehrlich's reagent assumed an orange, pink or red hue on contact with urine. The test was considered to be negative when the previously described change did not occur after the sample was mixed with the reagent.

Results

The clinical evaluation, treatment and results of the Hoesch test during hospitalization were as follows:

- Day +1: the patient presents with drowsiness, bradypsychia, bradylalia, visual hallucinations, sweating, constipation, facial flushing and inability to stand or walk without assistance. Hoesch test is positive. Treatment is started with heme arginate at 4 mg/kg, for which a central venous line is placed. (Figure 1a).

- Day +2, +3, +4: Clinical symptoms stay about the same (clinical stagnation), Hoesch test is positive. Treatment with

heme arginate at a dose of 4 mg/kg is continued. (Figure 1b)

- Day +5: signs of encephalopathy disappear. Involvement of the peripheral nervous system and dysautonomia persist (clinical improvement). Hoesch test is positive. Treatment with heme arginate at a dose of 4 mg/kg is continued. (Figure 1c)

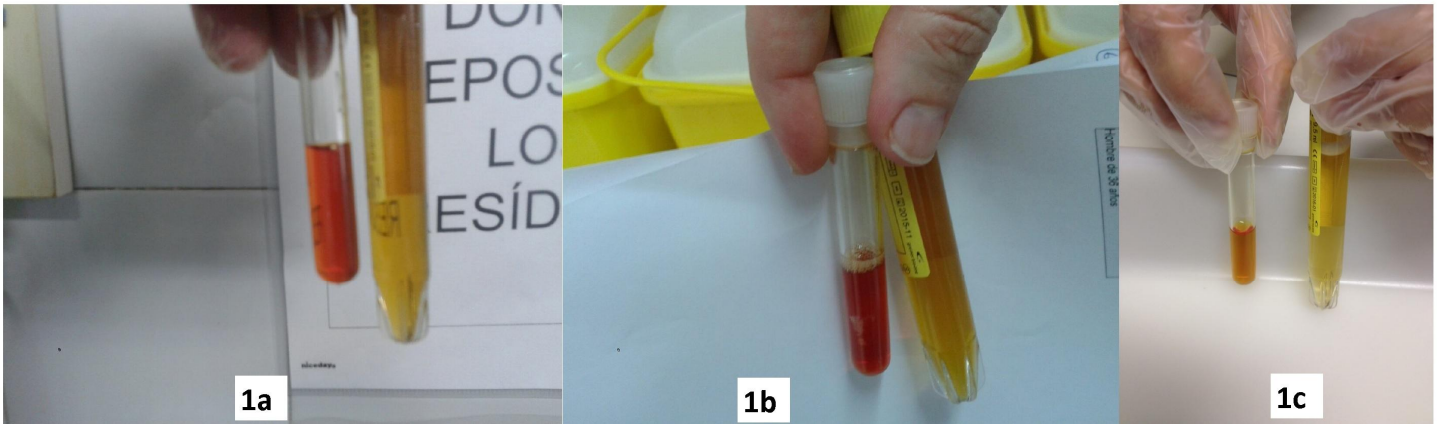

Figure 1. Hoesch Test (I)

- Day +6: hallucinations decrease, improvement in fluency of speech and thought. Hoesch test is positive. Continues to receive heme arginate at a dose of 4 mg/kg.

- Day +7: total disappearance of signs and symptoms. Hoesch test remains positive. Decision is made to discontinue heme arginate as clinical manifestations have disappeared. (Figure 2a).

- Days +8 to +18: absence of signs and symptoms. Hoesch test results are persistently positive. Untreated. (Figure 2b)

- Day +19: no clinical symptoms. Hoesch test is negative. Untreated. (Figure 2c)

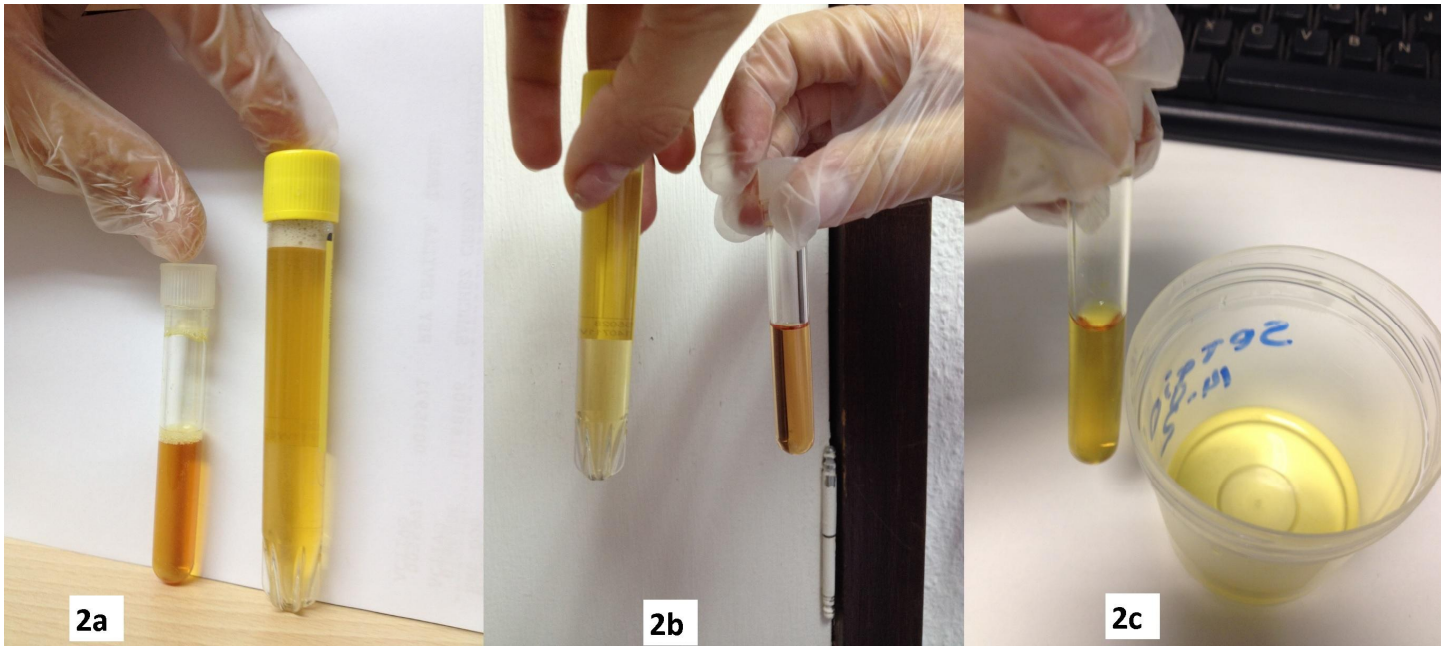

Figure 2. Hoesch Test (II)

Table 1. Porphyric crisis follow

Day	Symptoms	Treatment	(Hoesch test) Figure
1	Drowsiness, bradypsychia, bradilalia,visual hallucinations, sweating, constipation, acial flushing, inability to stand or walk	Heme arginate	(+) 1
2, 3, 4	Clinical stagnation	Heme arginate	(+) 2
5	Clinical improvement	Heme arginate	(+) 3
6	Clinical improvement	Heme arginate	(+)
7	Total disappearance of signs and symptoms	Heme arginate discontinuation	(+) 4
8-18	Absence of signs and symptoms	Untreated	(+) 5
19	Absence of signs and symptoms	Untreated	(-) 6

Discussion

Acute porphyria attacks are the most characteristic and severe manifestation of hepatic and mixed porphyrias. The severity is important, and the mortality rate is up to 10%, so early diagnosis and treatment are essential.

Acute porphyric attacks are also known as attacks of abdominal pain with associated neuropsychiatric features, as there may be manifestations of behavioral disturbances and disorders of the central (CNS), peripheral (PNS) and autonomic (ANS) nervous systems [2]. The most characteristic manifestations involve the ANS, such as abdominal pain, constipation, tachycardia, hypertension and sweating, all symptoms of dysautonomia. Disorders of the CNS include epileptic seizures and encephalopathy. Dysfunction of the PNS is characterized by predominantly axonal and motor impairment in the form of ascending polyneuropathy, which can even progress to paralysis of the respiratory muscles, usually preceded by dysphonia [2,6].

When faced with this array of symptoms or the occurrence of any one of the signs that are characteristic of the disease, we should consider a diagnosis of porphyria attack. This suspicion can be confirmed by performing a screening test for PBG in urine, a Hoesch test. In the event that the signs and symptoms are due to porphyria, the color of urine will turn red, pink or orange (wavelength around 700 nm). From a diagnostic standpoint, performing a Hoesch test is essential so that, if it is positive, appropriate treatment can subsequently be started.

It would be reasonable to think that, in the same way that a positive result substantially confirms a diagnosis of acute porphyria, after treatment has been found to be effective and the attack has subsided, the same test would show a negative result. The truth of the matter is that to date there are no objective data that can be used in conjunction with the clinical signs and symptoms to help us make the decision about how long a porphyric attack should be treated. It has been shown that PBG and delta-aminolevulinic acid (ALA) levels decrease with treatment with heme arginate, but no threshold has been identified below which clinical symptoms will disappear and even less a quantitative value that, together with the clinical symptoms, can be used to estimate the duration of treatment.

In a study in which ALA and PBG levels during the intercritical phase were evaluated, it was observed that they were elevated in some patients who nonetheless did not present any symptoms compatible with a porphyric attack [9].

At present, decisions regarding treatment duration are made in accordance with the patient's signs and symptoms. The recommended treatment regimen with heme arginate is 3-5 mg/kg/day for 4 days and the duration may be extended if clinical signs persist [5]. As mentioned above, the decision to prolong treatment is made on the basis of the patient's

clinical symptoms; if it is clear that they have disappeared, it follows that treatment may be suspended; if they persist, it seems advisable to continue treatment until they disappear.

In our case the signs and symptoms disappeared before results of the Hoesch test were negative and although treatment was ended when the clinical symptoms disappeared, in spite of Hoesch test results continuing to be positive, there was no relapse.

Our initial hypothesis was that in the same way that symptoms that are compatible with a positive Hoesch test can be used to diagnose a porphyric attack, the disappearance of the symptoms together with negative test results could mean the attack was over and therefore that it was possible to stop treatment. The objective was to assess the Hoesch test as just another variable when it comes to making decisions about treatment discontinuation, since its usefulness when determining whether to start treatment has been well established.

In our experience, upon analyzing a porphyric attack in an already known patient who in the past had presented with attacks that had required prolonged treatment with heme arginate is that, at the time of the diagnosis, the clinical symptoms are compatible with an attack and the results of the Hoesch test are positive, but after the symptoms resolve test positivity persist. Moreover, suspending treatment after the disappearance of the signs and symptoms, in spite of positive Hoesch test results, does not entail the recurrence of the symptoms.

It would therefore seem that, in conjunction with the clinical findings, the Hoesch test is essential to the initiation of treatment for a porphyric attack, but it is not of use when it comes to making decisions regarding the duration of treatment, which would depend on the clinical symptoms disappearance.

From this observation the big question arises as to why the Hoesch test remains positive even though there are no clinical signs indicative of a porphyric attack. It is possible that lower concentrations are needed for positive results on a Hoesch test than are necessary to induce symptoms, so this may be the reason for which symptoms disappear while positivity persists.

In face of these results, in one single case, the need arises to analyze the performance of the Hoesch test on a larger number of patients who suffer attacks of acute porphyria. If these results are confirmed, the usefulness of the Hoesch test would be limited to diagnosing the attack, but will be shown to have none for the monitorization during the treatment of the acute attack.

Conclusions

Nowadays we have to guide the duration of human hemin treatment with clinical symptoms previosly related as Porphyria with positive Hoesch test. It could be logical that if we have a positive test, we have enough reasons to treat with human hemin, but we have to know that actually, the place that corresponds to Hoesch test is the diagnosis of major porphyric attack, it does not take place as indicator of treatment duration.

The Hoesch test, an essential tool for diagnosing porphyria attacks, does not seem to be useful when taking decisions regarding treatment duration, so that for now and while we wait for this test to be performed in a larger number of patients suffering from acute porphyria attacks, treatment duration will depend on the duration of signs and symptoms.

Conflict of interest

Juan José Nava Mateos declares not to have conflict of interest.
Vicente Gómez del Olmo declares not to have conflict of interest.
Marta Rosas Cancio-Suárez declares not to have conflict of interest.
Raquel Besse Díaz declares not to have conflict of interest.
Olivia Sánchez Sánchez declares not to have conflict of interest.
Diego Cebrian Novella declares not to have conflict of interest.
Rafael Enriquez de Salamanca Llorente declares not to have conflict of interest.

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References

1. Raili Kauppineu. Porphyrias. Lancet 2005; 365: 241-52.
2. R. Enriquez de Salamanca Lorente. Porfirias. Farreras-Rozman, Medicina Interna. Volumen 1. Capítulo 4, páginas 22-29. 17ª edición. Barcelona: Elsevier, 2012.
3. Lamon JM, Fryklhom BC, Hess RA, Tschudy DP. Hematin therapy for acute porphyria. Medicine (Baltimore) 1979; 58 (3); 252-69.
4. No authors listed. Treatment of acute hepatic porphyria. Lancet 1978, Jun 24; 1 (8078): 1361-2.

5. Mustajki P, Nordmann Y. Early administration of heme argininato for acute porphyria attacks. Arch Internal Med 1993;13; 153 (17): 2004-8.
6. Walderburg M, Bonnot O, Mocellini R, Velakoulis D. The neuropsychiatrics of inborn errors of metabolism. J Inherited Met Dis 2013; 36: 687-702.
7. Lamon J, With TK, Redeker AG. The Hoesch test: Bedside Screening for urinary porphobilinogen in patients with suspected pophyria. Clin Chem 1979;20/11, 1438-1440.
8. A S Winkler, T J Peters, R D C Elwes. Neuropsychiatric porphyria in patients with refractory epilepsy: report of three cases. J Neurol Neurosurg Psychiatry 2005;76:380–383.
9. Ylva Floderus, Eliane Sardh, Christer Möller, Claes Andersson, Lillan Rejkjaer, Dan E.H. Andersson et al. Variations in Porphobilinogen and 5-Aminolevulinic Acid Concentrations in Plasma and Urine from Asymptomatic Carriers of the Acute Intermittent Porphyria Gene with Increased Porphyrin Precursor Excretion. Clinical Chemistry 2006;52:4 701–707.
10. F. Sedel, N. Baumann, J.-C. Turpin, O. Lyon-Caen, J.-M. Saudubray, D. Cohen. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. J Inherit Metab Dis 2007; 30:631–641.
11. Besur S, Hou W, Schmeltzer P, Bonkovsky HL. Clinically important features of porphyrin and heme metabolism and the porphyrias. Metabolites. 2014;3:4(4):977-1006.