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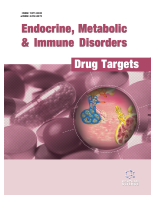
Cerebral Hypoperfusion in Hereditary Coproporphyria (HCP): A Single Photon Emission Computed Tomography (SPECT) Study



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Abstract: *Background*: Hereditary Coproporphyria (HCP) is characterized by abdominal pain, neurologic symptoms and psychiatric disorders, even if it might remain asymptomatic. The pathophysiology of both neurologic and psychiatric symptoms is not fully understood. Therefore, aiming to evaluate a possible role of brain blood flow disorders, we have retrospectively investigated cerebral perfusion patterns in Single Photon Emission Computed Tomography (SPECT) studies in HCP patients.

Materials & Methods: We retrospectively evaluated the medical records of patients diagnosed as being affected by HCP. A total of seven HCP patients had been submitted to brain perfusion SPECT study with 99mTc-Exametazime (hexamethylpropyleneamine oxime, HMPAO) or with its functionally equivalent 99mTc-Bicisate (ECD or Neurolite) according with common procedures. In 3 patients the scintigraphic study had been repeated for a second time after the first evaluation at 3, 10 and 20 months, respectively. All the studied subjects had been also submitted to an electromyographic and a Magnetic Resonance Imaging (MRI) study of the brain.

Results: Mild to moderate perfusion defects were detected in temporal lobes (all 7 patients), frontal lobes (6 patients) and parietal lobes (4 patients). Occipital lobe, basal ganglia and cerebellar involvement were never observed. In the three subjects in which SPECT study was repeated, some recovery of hypo-perfused areas and appearance of new perfusion defects in other brain regions have been found. In all patients electromyography resulted normal and MRI detected few unspecific gliotic lesions only in one patient.

Discussion & Conclusions: Since perfusion abnormalities were usually mild to moderate, this can probably explain the normal pattern observed at MRI studies. Compared to MRI, SPECT with 99mTc showed higher sensitivity in HCP patients. Changes observed in HCP patients who had more than one study suggest that transient perfusion defects might be due to a brain artery spasm possibly leading to psychiatric and neurologic symptomatology, as already observed in patients affected by acute intermittent porphyria. This observation, if confirmed by other well designed studies aiming to demonstrate a direct link between artery spasm, perfusion defects and related symptoms could lead to improvements in HCP treatments.

Keywords: Artery spasm, Hereditary Coproporphyria, perfusion defect, porphyrias, porphyric attack, SPECT (Single Photon Emission Computed Tomography).

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INTRODUCTION

Hereditary Coproporphyria (HCP) is a rare disease consequent to mutations of CPOX gene, localized to chromosome band 3q12 [1], that results in a dysfunction of the mitochondrial enzyme coproporphyrinogen oxidase [2] which catalyses the oxidative decarboxylation of coproporphyrinogen III to protoporphyrinogen IX in the heme synthesis pathway. Coproporphyrin as well as porphyrin precursors (porphobilinogen and aminolevulinic acid) accumulate, causing peripheral neuropaty, typically a motor neuropathy, and autonomic neuropathy often presenting with hypertension and tachycardia, psychiatric manifestations (depression), seizures and mental status changes [3].

Like the other hepatic (neurovisceral) porphyrias (Acute Intermittent Porphyria - AIP, Variegate Porphyria – VP, and ALA-dehydrase deficient porphyria), HCP may either remain asymptomatic in coproporphyrinogen oxidase defect bearers or suddenly appear with life-threatening attacks of neurovisceral symptoms characterized by abdominal pain (often simulating an acute abdomen), nausea, vomiting, constipation, muscle weakness, acute neuropathy, hallucinations, depression, anxiety and paranoia [3]. Attacks are often triggered by some drugs, particularly those leading to increased activity of the hepatic P450 system, alcohol, hormonal variations, and severe and prolonged dieting or fasting that boost heme synthesis. HCP attacks require specific immediate therapy with high doses of glucose and hemine. In absence of contraindications all porphyria patients are treated with low doses of acetylsalycilic acid (ASA), which improve microcirculation and have a mild analgesic effect for abdominal pain attacks. This drug has been proven safe in porphyria patients [4].

The severity of hepatic porphyrias is demonstrated by a death rate of 20- 25% within five years from the first attack [3]. This explains the clinical interest and the need of a careful follow-up.

Nowadays, the pathophysiology of both neurologic and psychiatric symptoms of HCP is not fully understood. A possible mechanism might involve an impairment in perfusion in different brain areas. These brain perfusion defects can be well evaluated by means of SPECT study whereas perfusion deficits in other parts of the body possibly leading to other symptoms such as abdominal pain can be less easy to show being other imaging techniques less efficient than is the SPECT at the brain level.

Therefore, aiming to evaluate a possible role of brain blood flow disorders, we have retrospectively investigated cerebral perfusion patterns in Single Photon Emission Computed Tomography (SPECT) studies in HCP patients. SPECT results have been compared with MRI and electromyography in order to demonstrate either a possible morphological expression of ischemic damage and perfusion defects-related functional abnormalities, respectively. In patient submitted to a second SPECT evaluation, we have compared the two studies aiming to demonstrate whether the changes were transient or permanent and the possible migration of the perfusion defects in other brain areas with possible clinical correlates.

MATERIAL AND METHODS

Study Population

This is a retrospective study evaluating a total of seven patients (3 Female, 4 Male, mean age 44 ± 19.6 yrs; age range 16-83 yrs) belonging to two different families (both the mothers and one child and four children respectively were affected) that had been admitted in our Institution ("Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy) because of the onset of acute abdominal, neurologic and psychiatric symptoms over a 18- yrs time period. A careful personal and familial medical history had been recorded in each patient. No other remarkable diseases were present with the exception of moderate hypertension treated with beta-blockers. In no case a history of coronary artery disease was on record. Table **1** summarizes the characteristics of the patients. Clinical examination and routine as well as specific laboratory tests had been performed (urinary levels of ALA and PBG). All subjects suffering from coproporphyria attacks had been studied in subacute (2-7 days) or intercritical conditions and, at SPECT test, they were on maltodestrine and/or hypertonic glucose. Furthermore, some patients received periodical treatment with hemine. Due to the presence of hypertension all subjects were on atenolol. Besides the SPECT study, the patients had been submitted to electromyography and brain MRI.

The study has been conducted in accordance with the Declaration of Helsinki. All the subjects had given their informed consent prior to being submitted to any of the described procedures, as well as they had accepted that their clinical, laboratory and imaging data would have been included in a database and possibly used for scientific purposes, as prescribed by the law in our country.

Mutations Analysis

After DNA isolation from leukocytes (QIAmp DNA Blood Mini Kit - QIAGEN, Netherlands), the entire coding region of the CPOX gene was amplified by polymerase chain reaction (PCR) and sequenced (ABI PRISM® 3130 xl Genetic Analyzer). HCP diagnosis was obtained by identification of two different missense mutations, maternally inherited in both families.

Imaging Techniques

All the subjects had been studied by Single Photon Emission Computed Tomography and, at the meantime, by electromyographic study and Magnetic Resonance Imaging (MRI) evaluation of the brain using a GE Signa 3 Tesla scanner (General Electric, Milwaukee, WI, USA). Besides standard sequences (Sagittal T1 FSGPR, Axial T2, Coronal T2, Axial FLAIR) four patients had been studied adding Diffusion Weighted Imaging (DWI).

In 3 patients the tomoscintigraphic study had been repeated for a second time after 3, 10 and 21 months, respectively. SPECT had been performed 30 minutes after intravenous administration of 740 MBq of 99m Tc-Exametazime (hexamethylpropyleneamine oxime, HMPAO)

Table 1. Patients' characteristics and results.

Patient (Pt)	Relationships	Gender	Age at SPECT Study	SPECT Results	Hemine *therapy*	Tracer	Fig
1	Son of pt 5 Brother of pts 2,3,4	M	38 y 7 m	Multiple little hypoperfusion areas in the whole cortex (+). Hypoperfusion of left frontal and temporal cortex and right frontal cortex(++)	No	ECD	
1 (2^{nd} study)		M	38 y 10m	Multiple diffuse little areas of hypoperfusion in the whole cerebral cortex(+) more evident in left frontal area (++)	No	ECD	
2	Son of pt 5 Brother of pts 1,3,4	M	37 y 5 m	Mild perfusion defect of right fronto-parietal cortex (+) and moderate perfusion defect of right temporal lobe pole (++).	No	ECD	1
2 (2^{nd} study)		M	38 y 3 m	Disappearance of the previously observed perfusion defect on right fronto-parietal cortex and onset of a new hypoperfused area on left fronto-parietal cortex. Hypoperfusion extension to the left temporal lobe pole (++).	No	ECD	2
3	Daughter of pt 5 Sister of pts 1,2,4	F	40 y 11 m	Mild hypoperfusion at right temporal lobe and parahyppocampal gyrus (+)	No	ECD	
4	Son of pt 5 Brother of pts 1,2,3	M	45 y 9 m	Little area of hypoperfusion at left fronto-temporal border close to insula.	Yes	ECD	
5	Mother of pts 1; 2; 3 and 4	F	82y 9 m	Right temporoparietal (++) and medial frontal gyrus (+) hypoperfusion	No	HMPAO	
6	Son of pt 7	M	15 y 8 m	Minimal perfusion defect of right frontal cortex and reduced perfusion at left parieto-occipital border (+)	Yes	ECD	3a
6 (2^{nd} study)		M	17 y 4 m	Disappearance of the previously observed perfusion defects and onset of a new minimal hypoperfused area on left fronto-parietal cortex (+).	Yes	HMPAO	3b
7	Mother of pt 6	F	34y6 m	Little diffuse areas of very mild hypoperfusion at frontal and temporal lobes (+)	No	HMPAO	

(+) mild hypoperfusion; (++) moderate hypoperfusion.

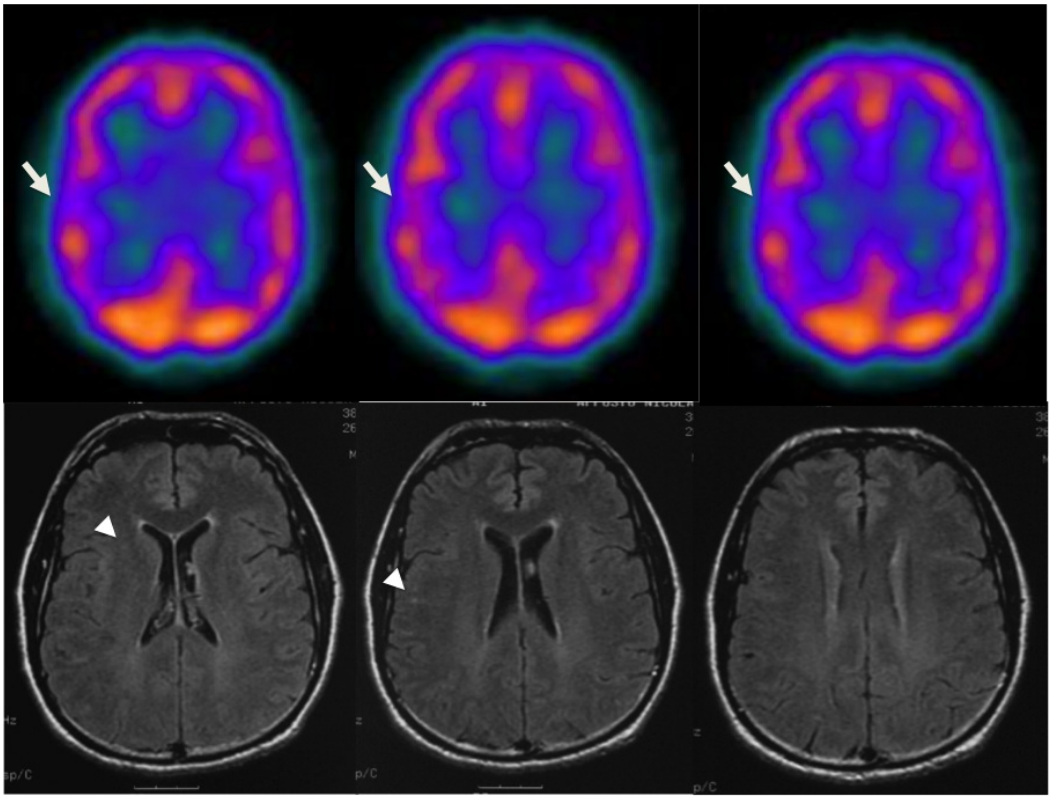
or of its functionally equivalent 99mTc-Bicisate (ECD or Neurolite). Relevations had been performed using tomographic gamma cameras (GE Millenium MG and GE OPTIMA NX for studies before 2007). Two experienced observers (20 yrs and 25 yrs) reviewed by consensus all SPECT images with full agreement whilst MR exams have been reported by an experienced neuroradiologist (15 yrs).

RESULTS

All patients showed mild to moderate brain perfusion defects at SPECT study, whereas severe defects were never observed. According with the usual practice, the evaluation of the severity of the perfusional abnormalities has been done on the basis of a personal evaluation expressed by the consensus of two experienced nuclear physicians [5,6].

The perfusion pattern resulted quite variable ranging from multiple bilateral mild perfusion cortical defects to moderate side perfusion cortical asymmetry with little perfusion defects. The most commonly affected areas were temporal lobes (all 7 patients), frontal lobes (6 patients) and parietal lobes (4 patients). Occipital lobe, basal ganglia and cerebellar involvement were never observed (Figs. **1**,**2**,**3**). In the three subjects who repeated SPECT study, modifications of the perfusion pattern were observed, with at least partial recovery of some previously hypo-perfused areas and appearance of new perfusion defects in other brain regions (Figs. **1**,**2**,**3**). In all patients electromyography resulted normal. MRI studies didn't show any pathological findings to be related with SPECT abnormalities, neither adopting DWI sequences. Only in one patient, axial FLAIR sequence showed minimal unspecific gliotic lesions in right frontal lobe, close to a hypo-perfused area detected by SPECT study performed in the same day (Fig. **1a**). The 1 year follow-up second SPECT evaluation showed a different SPECT perfusion pattern with no defects in previously affected region and a new hypo-perfused area in contralateral frontal lobe (Fig. **2a**). In the same subject, compared to the previous

a



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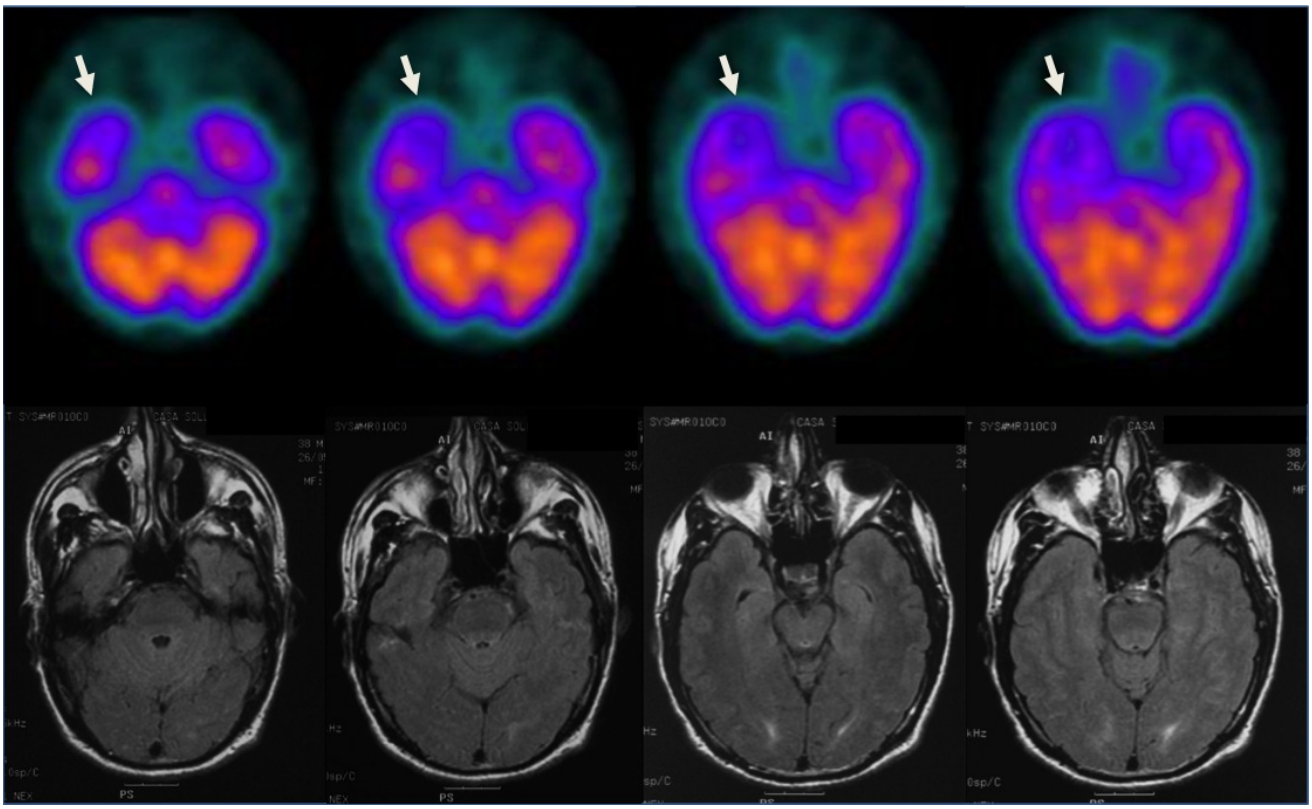

Fig. (1). Comparison of brain SPECT and MRI findings in a 37yo male (first study). a: mild perfusion defect of right fronto-parietal cortex (arrows) at SPECT. MRI FLAIR sequence shows only minimal unspecific gliotic lesions (arrowheads) close to the hypoperfused area detected by SPECT. **b**: moderate perfusion defect of right temporal lobe pole at SPECT study. No focal alterations detected with MRI.

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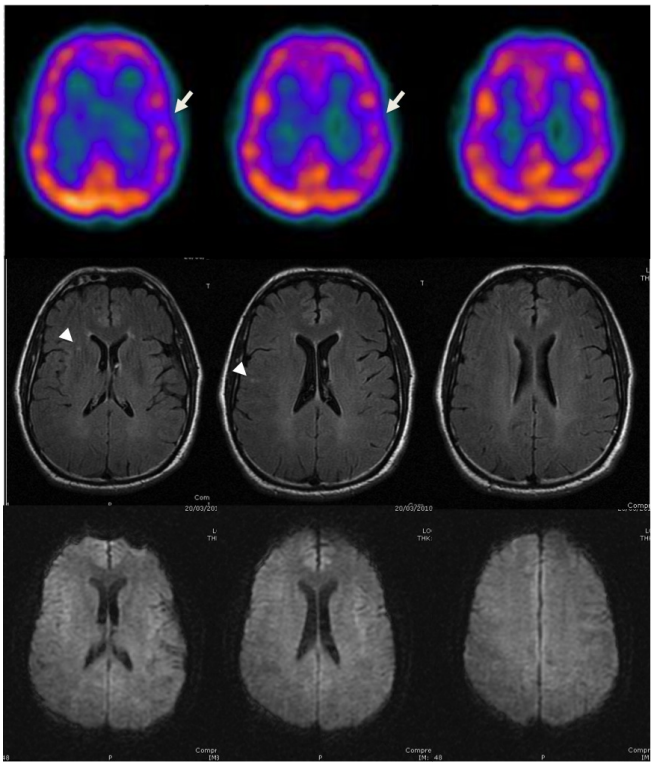

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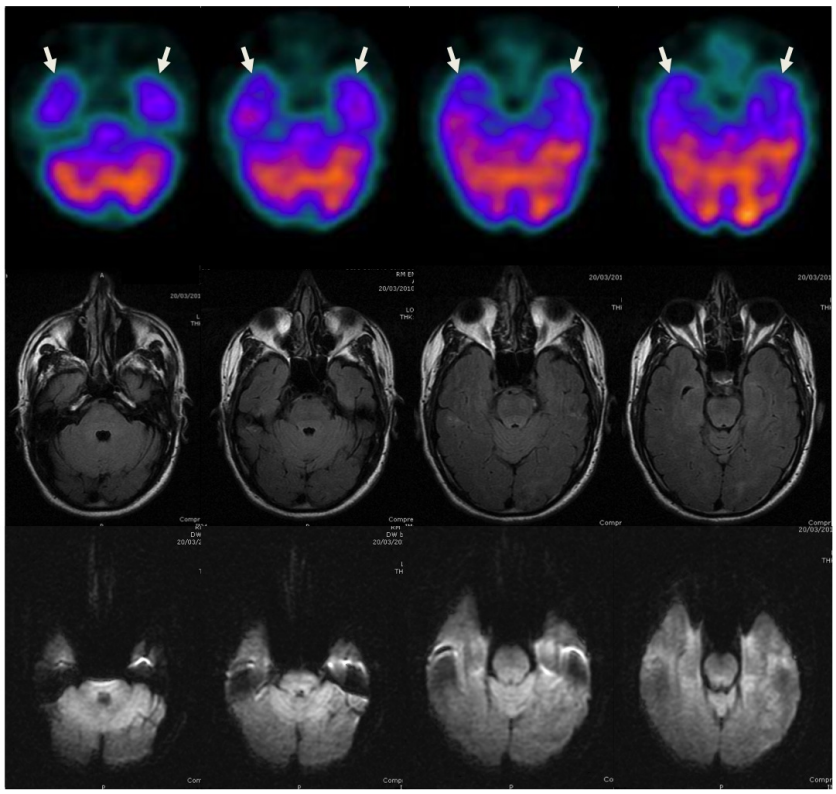

Fig. (2). Comparison of brain SPECT and MRI findings in the same patient of Fig. 1 (37yo male) at follow-up. a: disappearance of the previously observed perfusion defect on right fronto-parietal cortex and onset of a new hypoperfused area on left fronto-parietal cortex (arrows). MRI FLAIR shows no significant changes compared with the previous study (arrowheads). DWI shows no significant abnormalities. **b**: hypoperfusion extension to the left temporal lobe pole at SPECT study (arrows). No focal alterations detected with MRI (FLAIR and DWI).

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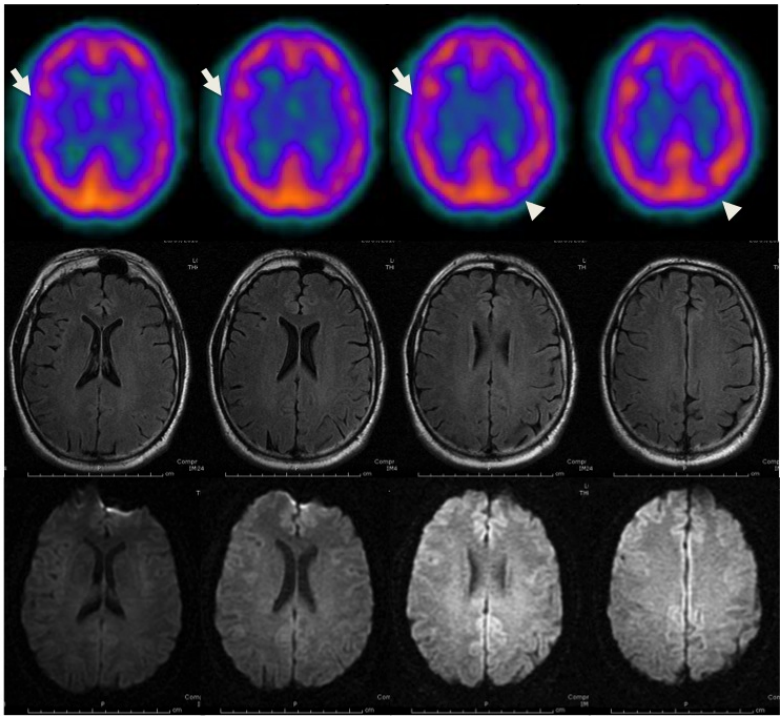

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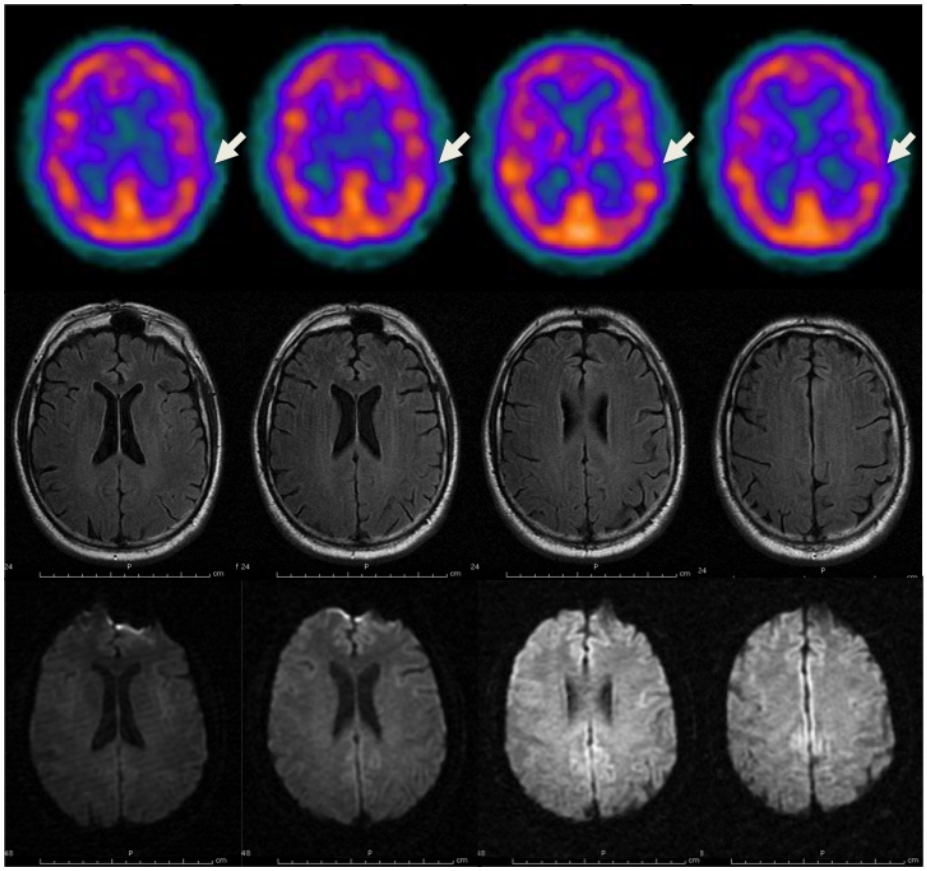

Fig. (3). Comparison of brain SPECT and MRI findings in a 15 yo male at baseline and at follow-up. a: Baseline: minimal perfusion defect of right frontal cortex (arrows) and *left parieto-occipital border* (arrowheads) at SPECT. No focal alterations detected with MRI (FLAIR and DWI). **b**: Follow-up: disappearance of the previously observed perfusion defects and onset of a new minimal hypoperfused area on left fronto-parietal cortex (arrows). No focal alterations detected with MRI (FLAIR and DWI).

study, the MRI didn't show any recent ischemic area in DWI sequences neither other findings (Fig. **2a**).

No correlation was found between ALA and/or PBG urinary levels and brain perfusion defects at SPECT study.

DISCUSSION & CONCLUSION

HCP symptoms, which are similar to those of AIP, include unexplained abdominal pain, severe constipation, systemic arterial hypertension and several neurological manifestations such as motor weakness, sensory loss, psychiatric problems, seizures, and mental and behavioural abnormalities [7]. Pathophysiology of porphyrias' symptoms still remains not fully understood. Some authors [8, 9] hypothesised that clinical pattern mainly result from the accumulation of porphyrin precursors as ALA (aminolevulinic acid) and PBG (porphobilinogen), as suggested by the clinical observation of the unique association of these molecules with diseases that present with neurovisceral attacks [10]. In an animal model ALA injection resulted in myocardial infarction [11].

It has also been reported that, in patients with acute porphyria but not in normal controls, ALA and PBG reduced the re-uptake and the accumulation of catecholamines. This has been proposed as the mechanism underlying both hypertension and tachycardia commonly observed during acute porphyria attacks [12]. In our opinion this mechanism could, at least partly, be involved in the determinism of the perfusion defects observed, possibly mediated by the spasm of brain arteries. At this regard, the lower concentration of catecholamines reported in cerebellum compared to other brain areas [13, 14] could explain the absence of perfusion defects in that region in our series because of the lack of cerebellar artery spasm.

In 1995 Kupferschmidt *et al*. [15] suggested that cerebral vasoconstriction in porphyrias could occur as a consequence of reduced NO levels due to a dysfunction of the nitric oxide synthase that is an heme-enzyme [16].

Besides nitric oxide synthase, other heme-enzymes disorders could theoretically be implicated in HCP. It is well known, for example, that polymorphisms of prostacyclin synthase, the heme-enzyme that catalyzes the synthesis of PGI2 from prostaglandin H2, are associated with essential hypertension, myocardial infarction, and cerebral infarction [17]. A CYP4F2 haplotype has also been reported to be associated to cerebral infarction [18]. Although heme synthesis disorders are biochemically different from polymorphisms of the aminoacidic sequence, the possible role of heme-enzymes dysfunction in acute (hepatic) porphyrias looks worth of further and specific studies.

Several authors reported the presence of cerebral ischemia in patients with AIP; Kupferschmidt *et al*. and Black *et al*. [15,19] described MR patterns ranging from mild ischemic area up to reversible lesions [20, 21]. Important brain perfusion defects in AIP have been recently described by SPECT by Totaro *et al*. [22] in a series of 15 patients.

All the above reported experiences could indicate that acute porphyrias are associated to brain perfusion disorders, possibly due to artery spasm, that can at least in part contribute to porphyria symptoms.

The SPECT perfusional pattern of the patients with HCP appeared comparable to that observed in patients with Acute Intermittent Porphyria both for the severity and distribution of the observed perfusional defects [22-24].

In our experience, the reversibility and the changes in time of the perfusion defects recorded in those of our patients in which the study was repeated strengthens the suspicion that in HCP, like in AIP, brain vasospasm could play an important role. At this regard it is noteworthy that cerebral vasospasm and stroke have been recently reported as a consequence of the exacerbation in a patient with hereditary coproporphyria [25]. To the best of our knowledge, no further evidence in the literature has been found about brain vasospasm in HCP, probably reflecting the lower prevalence of HCP compared with AIP [26] and, possibly, a less evident neurologic involvement in the former condition. Our study, demonstrating brain hypoperfused areas that may change in time, is consistent with the case reported by Mullin *et al*. [25] and strengthen the hypothesis that in hereditary coproporphyria vasospasm might contribute to the neurological manifestations observed. Since SPECT-detected perfusion abnormalities were usually mild to moderate, brain hypoxia was not sufficient to determine cytotoxic oedema detectable with MR-DWI.

Our study has some limitations, most of them relying in its retrospective and long-term nature. The mild changes in data collection for each subject reflect the long symptoms-free time-lapse which reduced patients' compliance with follow-up. Due to ethical reasons, no SPECT exams on healthy control subjects have been adopted. However, the presence of perfusional abnormalities reported in very young people (in our study one of our 7 patients was 16 y.o.) should strengthen our hypothesis. Another limitation could be found in the lack of SPECT and MRI studies performed during the porphyric attacks: patients' critical conditions were often unsuitable with the prolonged immobility required by both the techniques. Besides the lack of a control group, data about asymptomatic subjects were not available in our study.

In conclusion, the most important consideration that springs out of our data is the possible role of vasospasm in the pathophysiology of HCP, as already known for AIP. This strengthens the suspicion that also the painful abdominal symptoms observed in acute porphyria patients could be, at least in part, consequent to arterial spasms and to a consequent visceral, scattered ischemia. At this regard it is noteworthy the reported observation of vasoconstriction and renal infarction in a patient admitted for a variegate porphyria attack [27]. Therefore, in our opinion, prospective and cautious therapeutic tests with tolerated vasodilators could be justified in the management of porphyria patients with neurologic, psychiatric and abdominal symptoms.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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