

NEW SYMPTOMS IN A PATIENT WITH DIAGNOSED  
PORPHYRIA – UNTYPICAL CLINICAL COURSE  
OR ANOTHER DISEASE?  
EXTENDED DIFFERENTIAL DIAGNOSIS OF  
MULTIPLE SCLEROSIS

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ABSTRACT

**Introduction.** Acute liver porphyrias are caused by mutations of genes encoding the heme biosynthesis enzymes. A lack of any of these enzymes leads to a decrease in the heme level, which in each case is manifested by identical clinical symptoms. Nervous tissue is particularly susceptible to a depletion of heme levels. Three classical symptoms of a porphyria attack include: abdominal pain (as a manifestation of autonomic neuropathy), peripheral neuropathy, and psychic disturbances. Apart from the main symptoms, porphyria attacks may be manifested as various neurological disturbances, such as: bulbar palsy, epileptic seizures, psychic disturbances and focal symptoms of CNS damage. The intensity of individual symptoms can vary. Although neurological symptoms usually disappear after the attack, they may cause permanent deficits. Through involving CNS, porphyria can mimic other neurological disorders. Damage to the nervous system can be confirmed by additional examinations. Thus far, disseminated focal changes during the attack, which disappear after the regression of clinical symptoms, have been described in magnetic resonance imaging (MRI) scans of the brain. Spinal cord abnormalities in MRI scans have not been described yet, despite the fact that damage to the anterior horn associated with porphyria has been confirmed in literature. While examining cerebrospinal fluid during the attack, an elevated protein level has been noticed, so far without the presence of oligoclonal bands.

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Received 22.12.2010, accepted 4.02.2011

**Aim.** This paper aimed to demonstrate that porphyria should be considered in differential diagnosis of clinically isolated syndrome (CIS) and multiple sclerosis (MS).

**Materials and methods.** This paper is based on the case of a symptomatic patient who carried a mutation in one of the genes for porphyria, and who developed a clinical manifestation of focal damage to CNS. A differential diagnosis of porphyria and CIS, with a subsequent conversion to a clinically defined MS, was carried out. The results of additional examinations performed routinely in both disorders, the clinical picture and data from medical literature have been used in the analysis of this case.

**Case study.** The authors present the case of a patient with confirmed genetic porphyria, who was hospitalized for purposes of establishing a diagnosis due to weakened lower extremities. The patient manifested spastic lower extremity paresis, sensation disorders and urinary incontinence, which indicated spinal cord damages. An MRI scan of the thoracic spine revealed disseminated foci with contrast enhancement. A high level of proteins and oligoclonal bands were detected in the cerebrospinal fluid. On the basis of a new clinical picture (differing from the previous attack symptoms), prolonged symptoms, spinal cord lesions in MRI, and the presence of oligoclonal bands, CIS was diagnosed. Quick and complete recovery was obtained due to the administering of a steroid therapy. After several months, the patient reported a similar, passing episode, which, according to the authors, confirmed the diagnosis and an expected conversion to a clinically defined MS.

**Results and discussion.** Taking into consideration the clinical manifestation of spinal cord involvement untypical of porphyria, the detection of spinal lesions in an MRI scan, the presence of oligoclonal bands in the cerebrospinal fluid and the positive effect of steroid therapy, the authors believe that this described patient, who was a symptomatic carrier of a mutation in a gene for porphyria, developed CIS.

**Conclusions.** This reported case, supported by data from medical literature, shows that porphyria should be taken into consideration in any differential diagnosis of CIS and MS.

**Key words:** porphyria, clinically isolated syndrome (CIS), multiple sclerosis (MS)

## INTRODUCTION

Acute liver porphyrias are a group of genetically conditioned congenital diseases involving disturbances in the heme biosynthesis pathway. Mutations of the encoding genes lead to a decreased activity of the heme synthesis enzymes. The biosynthesis occurs in several stages, yet a decrease in the activity of any of these enzymes leads to, through elevated levels of substrates (delta-aminolevulinic acid, porphyrinogen, porphyrins) and a depletion of heme levels, identical clinical manifestations [11]. Three classical symptoms of

a porphyria attack include: abdominal pain (as a manifestation of autonomic neuropathy), peripheral neuropathy, and psychic disturbances. Apart from the main symptoms, porphyria attacks may be manifested as various CNS-induced neurological syndromes, such as: bulbar palsy, epileptic seizures, posterior reversible encephalopathy syndrome (PRES). This multiplicity of neurological symptoms stems from the fact that nervous tissue is particularly susceptible to a depletion of heme levels [15]. The intensity of individual symptoms is variable, which frequently delays a correct diagnosis. Because porphyria involves the central and peripheral nervous systems, it can mimic other neurological disorders, including multiple sclerosis (MS) [14]. Damage to CNS can be confirmed by the abnormal results of additional examinations. Disseminated demyelinating lesions detected in a magnetic resonance imaging (MRI) scan during an attack, which disappeared after the regression of clinical symptoms [1, 3, 9, 12], or resulted in permanent deficits [7] have been described. Demyelinating foci are found in patients between their porphyrias attacks, as well as in asymptomatic carriers of a mutated gene [10]. Abnormalities are also detected in cerebrospinal fluid examinations [2, 4, 10].

## **AIM**

This paper aimed to demonstrate that porphyria should be considered in differential diagnosis of clinically isolated syndrome (CIS) and multiple sclerosis (MS).

## **MATERIALS AND METHODS**

This paper is based on the case of a symptomatic patient who carried a mutation in one of the genes for porphyria, and who developed a clinical manifestation of focal damage to CNS. Differential diagnosis of porphyria and CIS, with a subsequent conversion to a clinically defined MS, was carried out. The results of additional examinations performed routinely in both types of disorders, and the clinical picture and data from medical literature have been used in the analysis of this case.

## **CASE STUDY**

A 29-year old patient was admitted to the Department of Neurology for purposes of establishing a diagnosis of strength weakness and lower limbs disability that had been present for 2 months, as well as urinary incontinence and sexual function disturbances. According to the patient, these symptoms appeared suddenly, and exacerbated rapidly within 2 days. Thus, he reported to the Outpatient Clinic of Neurology. When lower extremity paresis was detected during the neurological examination, the patient was referred to undergo MRI of the cervical and thoracic spine. These performed scans showed numerous foci in both sections of the spinal cord, which were hyperintense on T2-weighted images and isointense on T1-weighted images, and intensified after contrast medium administration. In the opinion of the radiologist describing the MRI scans, the images were not definite.

In his childhood, the patient was diagnosed with hereditary coproporphria, confirmed by DNA tests involving both him and the members of his family. He then manifested elevated levels of coporphyrin, uroporphyrin, 5,6,7-COOH porphyrin, and delta-aminolevulinic acid in the urine as well as a high level of coporphyrin I in the feces. Following an advised diet and avoidance of banned substances allowed the patient to achieve long-lasting intervals between porphyria attacks, which appeared every few years. The last episode had occurred a year before. Attacks were manifested typically as abdominal pain and a general weakness. Before the aforementioned problems appeared, the patient had not experienced any symptoms which might have suggested damage to CNS.

During the neurological examination performed on admittance to the Department, the following symptoms were detected: spastic lower extremity paresis, more intense in the right one, with exaggerated knee-jerk and ankle-jerk reflexes, and Babinski's sign on the right side, gait assisted with elbow crutches, lack of abdominal reflexes, left-sided hypesthesia beginning at the Th 8 level of the spinal cord downwards, and urinary incontinence.

Lumbar puncture was performed in the department. A high protein level – 126 mg% (norm ranges from 20–40 mg%) and the presence of oligoclonal bands type III were detected in the cerebrospinal fluid. This, according to the standards of the Charcot Foundation, confirmed intrathecal IgG synthesis. Other parameters of the cerebrospinal fluid were normal. The levels of anti-*Borrelia burgdorferi* and tick-borne encephalitis antibodies were low. An EMG examination excluded polyneuropathy. Visual evoked potentials (VEP) were normal. Due to technical reasons, an MRI scan of the head was not performed.

Considering the medical history, neurological symptoms and results of additional examinations, CIS was diagnosed. The patient received oral corticosteroids (Encorton) 60 mg/24 hours – unlike Solumedrol, this medication is allowed in porphyria. Physical rehabilitation was introduced. A significant improvement of gait efficiency and sphincter muscles function was achieved. The patient was discharged after 2 weeks of hospitalization, walking independently, without objective features of paraparesis. He was advised to continue therapy with Encorton, 60 mg/24 hours, reduced by 5 mg each day, and Ditropan, 3 × 5 mg. The patient returned to work abroad. 9 months later he informed medical personnel via a telephone call about the recurrence of the symptoms, of a lower intensity, which regressed without treatment after 2 weeks. The patient did not manifest symptoms typical of a porphyria attack, at this time. According to the attending physicians, this situation confirmed the correctness of the initial diagnosis, and the conversion of CIS to a clinically defined MS.

## RESULTS AND DISCUSSION

The case described therein served as a starting point for the attending physicians to consider the original cause of the symptoms and problems, and any abnormalities

detected in the performed additional examinations. The presence of porphyria, a disorder which can potentially involve CNS, necessitated a careful differential diagnosis and cautiousness when diagnosing a new disease.

The clinical picture was not typical of a porphyria attack. The most frequent symptoms of such an attack involve abdominal pain (in more than 95% of patients), tachycardia (80%), dark urine (about 75%) [2]. Symptoms of CNS being involved are observed in about 10% of patients [2, 16]. Such an attack can develop even over a few days and manifest new symptoms in time. Gurses et al. [7] have discussed the case of a patient who, after abdominal pain and dysuria lasting a week, developed symptoms of encephalopathy along with cortical blindness and quadriparesis. In this case, an attack resulted in permanent residual symptoms. Features of PRES are more frequently observed, when after the regression of a porphyria attack no abnormalities in the neurological examination have been found [1, 3, 9, 12]. Thus far, no symptoms of damage to the spinal cord have been reported. In the case described herein, these symptoms progressed, yet without changing their form. Stereotypical abdominal pain and weakness experienced previously were absent, whereas the symptoms of spastic paraparesis, due to their location, indicated damage to the spinal cord.

A performed MRI scan does not allow for establishment of a definite diagnosis. Many studies, already referred to, describe the presence of T2-weighted hyperintense disseminated foci. Such lesions have been detected both during porphyria attacks, and in interval periods. Aggarwal [1] has described the case of a woman who developed consciousness disturbance, and features of damage to her brain stem during an attack. An MRI scan showed disseminated foci which were hyperintense on T2-weighted images, and intensified after contrast medium administration. They were located along the gyrus both in the white and gray matter. After the administered treatment, a complete regression of the described abnormalities was observed in the follow-up MRI. However, most frequently, a porphyria attack is associated with reversible lesions typical of PRES with respect to their locations [3, 9, 12]. Bylesjö [4], when examining a group of 16 carriers of a mutation in a gene for acute intermittent porphyria, who were in an interval period between attacks, or in whom the disease had not yet revealed itself, detected in 2 persons hyperintense lesions on T2-weighted images, which were disseminated in the subcortical and periventricular white matter. One of these patients, with numerous documented attacks, had been treated for arterial hypertension for many years, which complicated the interpretation of the scan result. The other patient, apart from porphyria, did not have other comorbidities. Although changes involving loss of neurons with nuclear chromatolysis in anterior horn cells of the spinal cord have been documented in histopathological tests [6, 8], thus far lesions detectable in the spinal cord MRI scan during or between attacks have not been reported.

Both in the case of MS, and during porphyria attacks, abnormalities in the cerebrospinal fluid are observed. However, it is generally believed that in porphyria levels

of protein are usually normal or slightly elevated. Latorre and Munoz [13] analyzed 37 patients during porphyria attacks. Elevated levels of protein in the fluid were assayed in 21 patients (67%). Such a tendency is not observed between the attacks. Bylesjö detected only 1 case with a slightly elevated protein level in 16 carriers of the mutated gene. In the disease entity discussed herein, cases of significantly elevated levels of proteins in the cerebrospinal fluid have not been reported thus far. The presence of oligoclonal bands has been described only in patients with synchronous MS and porphyria [4].

## CONCLUSIONS

Taking into consideration the clinical manifestation of spinal cord involvement untypical of porphyria, the detection of spinal lesions in an MRI scan, the presence of oligoclonal bands in the cerebrospinal fluid and the positive effect of steroid therapy, the authors believe that this described patient, who was a symptomatic carrier of a mutation in a gene for porphyria, developed CIS. The criteria for recognizing CIS were met – the first clinical episode of focal damage to CNS and lesions detected in the MRI scan. Some doubts could have arisen from a very rare likelihood of two comorbidities: genetic, and so certain confirmation of porphyria, elevated levels of protein in the cerebrospinal fluid also found in porphyria, and a variety of untypical manifestations of porphyria reported in literature. The patient's further history, with a recurrence of the disease's symptoms indicates, in our opinion, a transformation to a clinically defined MS.

This reported case, supported by data from medical literature, shows that porphyria should be taken into consideration with respect to the differential diagnosis of CIS and MS.

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