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Tremor and Other Hyperkinetic Movements

Case Reports

Hereditary Coproporphyria Associated with the Q306X Mutation in the Coproporphyrin Oxidase Gene Presenting with Acute Ataxia

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Abstract

Background: Hereditary coproporphyria (HCPO) is a low-penetrance, autosomal dominant, acute hepatic porphyria characterized by the overproduction and excretion of coproporphyrin. The most common neurological manifestations of this entity include peripheral, predominantly motor dysfunction, and central nervous system dysfunction. Ataxia associated with HCPO has not been reported previously. The aim of this article is to report a patient with HCPO presenting with acute ataxia.

Case Report: We describe a 44-year-old patient presenting clinically with acute ataxia who was diagnosed with HCPO; mutations were analyzed in the *coproporphyrin-oxidase III* (*CPOX*) gene in the patient and in six asymptomatic first-degree relatives.

Discussion: The patient was heterozygous for a mutation causing the amino acid exchange Q306X in the *CPOX* gene. No relatives carried the same or another mutation in the *CPOX* gene. HCPO should be considered in the differential diagnosis for patients presenting with ataxia.

Keywords: Ataxia, porphyria, hereditary coproporphyria, *CPOX* gene, mutations

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Introduction

Porphyrias are metabolic diseases that develop from either inherited or, more infrequently, acquired disturbances of heme biosynthesis, leading to an overproduction of heme precursors in liver and bone marrow. Porphyrias are divided into acute hepatic, chronic hepatic, and erythropoietic types depending on the main site of expression of the enzymatic defect. Eight enzymes are involved in the eight steps of heme biosynthesis, and deficiencies in seven of them (except the delta-aminolevulinic synthase, responsible for the first step) each correlate with a specific form of porphyria.[1,2]

Patients suffering from acute porphyrias share a common clinical symptom of acute, severe abdominal pain attacks. In addition, symptoms such as nausea, vomiting, hypertension, tachycardia, and hyponatremia are present in most porphyric crises. Severe or prolonged attacks are accompanied by peripheral, predominantly motor dysfunction, and central nervous system dysfunction.[3] The presence of light-induced skin symptoms due to the dermal accumulation of the photosensitizing porphyrins, mainly blisters, ulcers, and skin fragility, are common in some acute porphyrias.[3]

Hereditary coproporphyria is a low-penetrance, autosomal dominant, acute hepatic porphyria characterized by the overproduction and excretion of coproporphyrin. The disease is the result of deficient activity of the mitochondrial enzyme coproporphyrinogen oxidase (CPOX, EC1.3.3.3) as a consequence of the inheritance of mutations in the *CPOX* gene (chromosome 3q12; OMIM 612732, gene ID 1371). In most cases, enzyme activity is reduced to nearly 50% in heterozygotes. Clinical crises are characterized by an acute polysymptomatic syndrome with abdominal, cardiovascular, neurological,

and psychiatric symptoms; nearly 20% of patients may experience photosensitivity.[1,3,4] At least 36 different mutations in the *CPOX* gene, with a high proportion of missense mutations, have been described.[5–7] We report a patient who was diagnosed with hereditary coproporphyria associated with a mutation in the *CPOX* gene presenting with acute ataxia.

Case report

The propositus was a 44-year-old male. He was a heavy smoker (60 cigarettes per day) and a moderate ethanol consumer, but had no other medical antecedents of interest. He did not consume drugs or herbal. He was admitted to the hospital for sudden onset of dizziness, severe gait unsteadiness, and difficulty with speech. The previous day he had been painting a metallic staircase with red lead paint. General examination revealed no abnormalities. Neurological examination showed scanning speech (considerably slow and dysarthric speech with pronounced slurring, most words being understandable), a mild vertical skew deviation of eyes without nystagmus, severe gait and trunk ataxia (the patient could only walk assisted by another person, gait speed was extremely low, he was unable to stand with feet together but was able to stand in a natural position with considerable sway and corrections, and he had moderate oscillations of the trunk and legs while sitting), mild dysmetria, and mild action tremor in the finger-to-nose and the finger-to-finger tests; moderate dysmetria and mild action tremor in the heel-to-knee test, and moderate dysdiadochokinesia for pronation supination alternating movements. The basal scores of the International Cooperative Ataxia Rating Scale (ICARS)[8] are given in Table 1.

Blood count, routine biochemistry; copper and iron metabolism studies; and serum levels of thyroid hormones, vitamins A, B_1, B_6, B_{12}, E, folic acid, proteinogram, immunoglobulins, C_3, and C_4 were normal. Serological studies for syphilis; Brucella; Borrelia; hepatitis A, B, and C; HIV, herpesvirus simplex 1 and 2, herpesvirus zoster; cytomegalovirus; Epstein–Barr virus; and measles were negative. Antinuclear antibodies, anti-Sjögren syndrome A and B, antineutrophil cytoplasmic, antigliadin antibodies, and cryoglobulins were negative. Tumor markers, including carcinogenic embryogenic antigen; alpha-fetoprotein; carbohydrate antigen (CA)125, CA19-9, and CA15-3; neuron-specific enolase; and prostatic-specific antigen were negative. Anti-Yo and anti-Hu antigens were negative both in serum and in cerebrospinal fluid (CSF). A test for 14-3-3 protein in CSF was also negative.

Brain computed tomography (CT) scan, brain magnetic resonance imaging, and thoraco-abdomino-pelvic CT scan were normal. Routine CSF analysis showed no abnormalities. Electromyography and nerve conduction studies were normal. Molecular genetic studies for Friedreich's ataxia; spinocerebellar ataxias (SCAs) 1, 2, 3, 6, 7, 12, and 17; and dentate-rubro-pallido-luysian atrophy were negative. Serum levels and 24-hour urinary excretion of lead were normal. The measurement of urinary excretion of porphyrins and their precursors showed a marked increase in excretion of coproporphyrins (1478 μg/24 hours; normal values 0.0–160.0 μg/24 hours) and total porphyrins (1616 μg/24 hours, normal values 0.0–200.0 μg/ 24 hours), a moderate increase in uroporphyrin excretion (138 μg/24 hours, normal values 0.0–60.0 μg/24 hours), a mild increase in excretion of porphobilinogen (2.53 mg/24 hours, normal values 0.0–2.0 mg/24 hours), and decreased concentration of delta-aminolevulinic acid (0.12 mg/g of creatinine; normal values 1.0–7.0 mg/g of creatinine).

The patient was treated with intravenous heme arginate (Normosang, 250 mg per day) for 10 days. This treatment led to a moderate clinical improvement of ataxia as assessed with ICARS[8] (pre- and post-treatment scores, 15 days after the onset of the treatment, are given in Table 1) and normalized values of urinary excretion of coproporphyrins (155 μg/24 hours), uroporphyrins (30 μg/24 hours), and total porphyrins (195 μg/24 hours). Two months later, the patient developed a severe behavioral disorder with aggressiveness, which resulted in divorce, and follow-up was lost.

We investigated the presence of mutations in all *CPOX* gene exons in the propositus: his mother aged 76 years (the father was deceased); one of his two brothers, aged 47 years; and his four sons, aged 11, 9, 7, and 5 years. All the relatives of the propositus were asymptomatic and provided written informed consent to this analysis (in the case of the children, written informed consent was provided by their mother).

DNA was isolated from peripheral lymphocytes. Sequencing analysis was performed as follows: first, fragments comprising the whole exon and the 5′- and 3′- flanking regions were amplified using the primers described in Table 2, then amplified fragments were analyzed by direct sequencing as described elsewhere.[9] Sequencing analyses were repeated in triplicate. Details for amplification conditions and oligonucleotides utilized for sequencing analyses are available on request.

The propositus was heterozygous for the mutation causing the amino acid exchange Q306X (exon 4) described elsewhere.[7] None of the patient's relatives had *CPOX* gene mutations.

Discussion

Our patient presented with acute ataxia following exposure to industrial red lead paint. Etiological studies on possible causes of hereditary or acquired ataxias were negative. However, because urine analysis showed a marked excretion of coproporphyrins and of total porphyrins, the patient was diagnosed with hereditary coproporphyria. This clinical entity is considered a very rare disease in Spain, where to our knowledge only six cases have been reported to date.[6,10,11] The rationale of testing this patient for porphyria was the exposure of the patient to red lead paint, which could act as a trigger of acute porphyria.[12,13]

Although we cannot rule out the association of ataxia and biochemical features of hereditary coproporphyria in our patient as coincidental, the clinical improvement of ataxia after treatment with heme arginate (together with improvement in biochemical parameters) seems to support this association. Prior to the development of ataxia, our patient had never suffered from recurrent abdominal pain or experience any skin or cardiovascular symptoms or symptoms suggesting peripheral or central nervous system dysfunction.

Table 1. Scores of the International Cooperative Ataxia Rating Scale (ICARS) before Treatment with Heme Arginate and 2 Weeks After Treatment

ICARS Subscale	ICARS Item	Pre-treatment Score (Day 0)	Post-treatment Score (Day 15)
Posture and gait disturbances	Walking capacities	7/8	5/8
	Gait speed	3/4	2/4
	Standing capacities, eyes open	4/6	3/6
	Spread of feet in natural position without support, eyes open	3/4	2/4
	Body sway with feet together, eyes open	3/4	2/4
	Body sway with feet together, eyes closed	3/4	2/4
	Quality of sitting position	2/4	1/4
	Posture and gait score (static score)	25/34	17/34
Kinetic function	Knee-tibia test	6/8	2/8
	Action tremor in the heel-to-knee test	2/8	2/8
	Finger-to-nose test: decomposition and dysmetria	4/8	2/8
	Finger-to-nose test: intention tremor of the finger	2/8	2/8
	Finger–finger test: action tremor and/or instability	4/8	2/8
	Pronation supination altering movements	4/8	2/8
	Drawing of the Archimedes spiral on a pre-drawn pattern	2/4	2/4
	Kinetic score (limb coordination)	24/52	14/52
Speech disorders	Dysarthria: fluency of speech	3/4	1/4
	Dysarthria: clarity of speech	2/4	1/4
	Dysarthria score	5/8	2/8
Oculomotor disorders	Gaze-evoked nystagmus	0/3	0/3
	Abnormalities of the ocular pursuit	1/2	1/2
	Dysmetria of the saccade	1/1	1/1
	Oculomotor movement score	2/6	2/6
	Total ataxia score	56/100	35/100

Table 2. Primers Used to Amplify the Seven Exons of the *CPOX* Gene

Fragment	Forward	Reverse
Exon 1	AGCTCGCCGGCTCAATACTC	TGTGGGTACCCCCTACCTAC
Exon 2	GATTTGGGAAACGGGAAAAT	GGGCAAAATAAGGTTTGCAG
Exon 3	GCCGCACGTTGACAAATACT	TTGCCTTTACATTGCCTCCT
Exon 4	TTCTGCCTAGGCCTTACTGG	TGTAATTTTGGGGTCATGAAA
Exon 5	ACCTGAAAGGCTCAC	TAAGAGCTGCTCCAC
Exon 6	GCTGTAGGCTGGTGTCCTCT	TTGGGAATTGGGAGTGTAGG
Exon 7	TGTGGCACAAATGAAAACTTTA	TGCTTTTGTTTTGGACATGC

The mutations analysis performed on the patient and his asymptomatic first-degree relatives revealed that he was the only member of the family who had a previously reported mutation in the *CPOX* gene (Q306X).[7] To our knowledge, the presentation of hereditary coproporphyria with acute ataxia has not been reported. The possibility that this symptom could be related to the presence of the Q306X mutation is unclear. Urinary analysis of porphyrins could be useful in the study of patients with acute ataxia.

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