Cellular and Molecular Biology [TM] **55**, N°2, 36-39
DOI 10.1170/T850

ISSN 1165-158X
2009 Cell. Mol. Biol.[TM]

ASSOCIATION BETWEEN PORPHYRIA CUTANEA TARDA AND BETA-THALASSEMIA MAJOR

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Received, May 11th 2009; Accepted May 26th, 2009; Published July 1st, 2009

Abstract – The paper describes the first two cases of porphyria cutanea tarda associated with beta-thalassemia major. The clinical course of two female patients affected by beta-thalassemia major was complicated by the onset of porphyria cutanea tarda. Both patients were also suffering from hepatitis C virus infection, iron overload and anemia. We discuss about the role performed by some of these conditions in triggering overt porphyria cutanea tarda. An improvement of the clinical and biochemical picture of porphyria cutanea tarda in both patients was obtained with chloroquine therapy given that their chronic anemia did not permit phlebotomy.

Key words: Porphyria Cutanea Tarda, beta-thalassemia, Hepatitis C virus infection, Iron overload, Chloroquine.

INTRODUCTION

Porphyria cutanea tarda (PCT) (MIM 176100), the most common form of porphyria, arises from reduced activity of uroporphyrinogen decarboxylase (URO-D), one of the enzymes of the heme biosynthetic pathway that sequentially converts uroporphyrinogen to coproporphyrinogen (9). The disease phenotype results from accumulation of uroporphyrins in liver and blood. Uroporphyrins are photoactive molecules and are responsible for the photodermatitis that occurs on sun-exposed areas. The main clinical features of PCT include increased skin fragility, blisters, erosions and facial hypertrichosis. Liver disease is seen in almost all cases of PCT. Two major forms of PCT are described: sporadic (s-PCT) and familial (f-PCT). In the most common sporadic form, the enzyme activity is decreased only in the liver whereas in the familial form the enzymatic defect is also present in other cell types, such as erythrocytes (9). In all PCT types, the enzymatic defect itself is not sufficient to produce a PCT phenotype and needs cofactors. Well-recognized risk factors for PCT onset include principally hepatitis C virus (HCV) infection, (13,14) iron overload, alcohol and exogenous oestrogens (2).

Beta-thalassemia major (TM) is an inherited homozygous condition characterized by reduced or absent synthesis of the beta globin chains of haemoglobin, due to different defects of beta globine gene, with severe anemia in relation to a largely ineffective erythropoiesis. Severe anemia is treated with frequent blood transfusions. Heart, liver and endocrine glands iron overload and HCV infection are frequent complications in polytransfused thalassemic patients.

Abbreviations: **HCV**, hepatitis C virus; **PCT**, porphyria cutanea tarda; **f-PCT**, familiar- porphyria cutanea tarda; **s-PCT**, sporadic-porphyria cutanea tarda; **TM**, beta-talassemia major; **URO-D**, uroporphyrinogen decarboxylase.

CASE REPORT

Patient 1

A 45- year-old caucasian woman, consecutively treated at St. Eugenio Hospital of Rome, had been diagnosed with TM (β^0 39; IVS 1-1 genotype) at the age of 2 when she began transfusion therapy. In 1979, when she was 15, she started iron chelation therapy with subcutaneous desferioxamine infusion. Oestrogens and l-thyroxine replacement therapy were started for primary amenorrhoea and hypothyroidism at the age of 19. In 1998 (34 years old) active hepatitis related to HCV infection (genotype 1b) was diagnosed and she was successfully treated with alpha-interferon for

one year. At that time, serum ferritin was about 500 ng/ml but fifteen months after interferon therapy had been stopped the patient showed signs of relapse. Serum ferritin level raised to 2100 ng/ml for a decreased compliance to desferioxamine and liver iron concentration (LIC) evaluated by Squid was 11.9 mg/gr/dw. Liver ultrasound and alfa-fetoprotein were performed to exclude hepatocellular carcinoma development. During the relapse of active hepatitis, skin fragility, hyperpigmentation and hypertrichosis of the temporal regions appeared. The suspect of PCT was confirmed by biochemical analyses in January 2001. Total urinary porphyrins (6) were 1.68 mg/24h (normal values: <0.150 mg/24h), and urine HPLC (15) showed a prevalence of 8 and 7-COOH porphyrins; total serum porphyrins (5) were raised to 0.138 mg/L (normal values: <0.004 mg/L) and plasma fluorimetric emission scanning test (19) gave a peak at 620 nm. She was screened for hereditary haemochromatosis (4) and resulted heterozygous for Histidine 63 Asparagine (His 63 Asp) mutation. Genetic testing for URO-D gene, performed by PCR-amplification and direct sequencing on genomic DNA from peripheral blood, detected a heterozygous two bp deletion, c.637 –132delTA (intron 6), not listed in Human Gene Mutation Database. Erythrocyte URO-D activity (8) was normal.

Oestrogens therapy was discontinued and therapy with chloroquine immediately started (125 mg, twice weekly) and continued for one year till the normalization of biochemical and clinical picture. She went on with the usual iron chelation therapy with subcutaneous desferioxamine (35 mg/Kg for 12 hrs/six days weekly). During chloroquine therapy, urine and serum samples were monthly collected and evaluated for the following analyses: total urinary porphyrins, total serum porphyrins and liver function tests. Only a transient elevation of urinary and serum porphyrins was early detected, followed by a gradual normalization during one year. In the same period of time there were no significant changes in liver function tests. Resolution of the skin fragility, hypertrichosis and hyperpigmentation was observed.

Patient 2

A 30-years-old caucasian woman, affected by beta-thalassemia major (β°39/β°39 genotype), started transfusion therapy at age of 1 and iron chelation therapy with desferioxamine at 2. When she was 10, HCV infection (1b genotype) was diagnosed. At the age of 18, she started oral contraceptive but she discontinued three months later because of hyperglycemia. Active hepatitis C was detected only at 26 when her serum ferritin was about 2500 ng/ml and LIC evaluated by Squid 18 mg/gr/dw. Alpha-interferon and ribavirine therapy was immediately administred and continued for one year till the resolution of hepatitis. Howewer, three months later, active hepatitis relapse was detected. When she was 28, because of cardiac ejection fraction decrement related to iron overload, she was submitted to combined iron chelation therapy with desferrioxamine, 40 mg/Kg for 12 hrs/six days weekly, and deferiprone, 75 mg/Kg seven days/week. After one year of therapy, ferritin level decreased from 3500 ng/ml to 800 ng/ml.

Two years later, in June 2008, she was hospitalized at St Eugenio Hospital for the development of agranulocytosis due to adverse event deferiprone-related. The patient was treated with rHuG-CSF (150 mcg/m2/day). Iron chelation therapy was interrupted and the value of serum ferritin rapidly increased to 5700 ng/ml. Two months later, she started again subcutaneous infusion of desferrioxamine (40 mg/Kg/12 hrs/ seven weekly).

In July 2008 the patient showed hypertrichosis of the temporal regions and a single little crust lesion on the right hand. The suspicion of PCT was confirmed by biochemical analyses. Total urinary porphyrins (6) were 0.56 mg/24h (normal values: <0.150 mg/24h), and urine HPLC (15) showed a prevalence of 8 and 7-COOH porphyrins; total serum porphyrins (5) were 0.028 mg/L (normal values: <0.004 mg/L) and plasma fluorimetric emission scanning test (19) gave a peak at 620 nm. She was screened for hereditary haemochromatosis (4) and resulted wt/wt. Genetic testing for URO-D gene, performed by PCR-amplification and direct sequencing on genomic DNA from peripheral blood, was unable to detect any mutation. Chloroquine therapy, started at the same dosage of the previous patient (125 mg, twice a week), was followed by a transient increase of total urinary porphyrins and of transaminases. Two months after the beginning of chloroquine therapy, serum total porphyrins and liver function tests were normal, whereas only total urinary porphyrins remains slightly incremented (0,19 mg/24h). To date she is continuing chloroquine therapy.

DISCUSSION

In TM patients, the correct application of transfusional and iron chelation therapies has determined an increase of the average life span and an improvement of the quality of life (3). Notwithstanding these patients are still exposed to secondary pathologies such as iron overload and chronic HCV hepatitis. To this regard, the described cases have developed PCT as result of one or more pathologies secondary to TM. It is well known that PCT can be silent until triggering factors make it clinically manifest. To this regard, HCV infection (13,14), iron overload (18) and exogenous oestrogens (2) are known to be associated with the development of PCT in susceptible individuals.

To date and to our knowledge, only association between beta-thalassemia carriers and PCT had been described (12,17) and our two patients have to be considered the first cases of association between PCT and beta-thalassemia major. In our first case, PCT developed during the relapse of HCV-related hepatitis, when concomitant severe iron overload occurred (serum ferritin 2100 ng/ml). To be noted that during the first episode of active HCV hepatitis, two years before, iron overload was not so remarkable (serum ferritin 500 ng/ml). Therefore, iron was probably the most important PCT triggering factor in this patient, and the co-existence of HCV infection and of exogenous oestrogens should be considered as less relevant for phenotypic expression of the disease.

In the second patient HCV infection was diagnosed when she was 10. Active hepatitis occurred only sixteen years later, when she was successfully treated with alpha-interferon and ribavirine. After the end of the therapy a relapse of active hepatitis occurred , serum ferritin was about 2500 ng/ml but no PCT symptoms appeared. At 30, iron chelation therapy was interrupted for agranulocytosis, and serum ferritin rapidly increased from 2500 ng/ml to 5700 ng/ml. One month later the patient developed PCT symptoms. We assume that iron overload was the main PCT triggering factor in this case too.

To be noted that chronic anemia due to beta-thalassemia did not permit phlebotomy as therapy for PCT (16). Chloroquine was therefore the first choice therapy. They were treated with 125 mg twice a week (1) and monitored monthly for urinary and serum porphyrins and for transaminases. Chloroquine at this dosage was not hepatotoxic, as showed by liver function tests during the course of therapy. Only during the first phase of therapy urinary porphyrin excretion transiently increased, indicating a phase of mobilization, as previously described in the current literature (11). Resolution of the clinical and biochemical picture was obtained in the first case, whereas in the second patient, only an improvement was detected.

In conclusion, we describe the first two cases of association between porphyria cutanea tarda and beta-thalassemia major. Severe iron overload is probably the main PCT triggering factor in both patients. Low dose chloroquine is to be considered the first choice therapy when association between the two diseases occurs.

ACKNOWLEDGEMENT

We thank Dr Paolo Cianciulli and Dr. Francesco Sorrentino, Centro Microcitemie, Ospedale Sant'Eugenio, Rome, Italy, for submitting to our attention the patients.

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