Familial Mediterranean Fever Phenotype II in Greece

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Familial Mediterranean fever is manifested by recurrent crises of abdominal pain and arthralgias. A late complication of the disease may be renal amyloidosis; this complication however, is rarely the presenting symptom of the phenotype II form of the disease. We report such a case in a Greek patient who presented with nephrotic syndrome due to renal amyloidosis.

Patient Description

A 65 year old woman from Corfu island (Ionian Sea, northwest Greece) was referred for investigation of a severe nephrotic syndrome that appeared several weeks earlier. Her ethnic origin was Greek and her religion Christian Orthodox. There was a generalized edema that was more evident on both ankles. Urine testing revealed severe proteinuria (7 g/dl protein loss). Her past medical history was unremarkable apart from a moderate depression necessitating anti-depressive drugs (mianserin). There was no hypertension, diabetes or any indication of a systemic disease. Abdominal ultrasonography revealed a symmetric bilateral renal enlargement. Renal biopsy and light microscopy did not reveal any gross amyloid deposition by Congo stain; however, histochemistry indicated the presence of AA type amyloid, thus confirming the diagnosis of renal amyloidosis (amyloid A component MO 759, DAKO, Denmark).

A thorough investigation to detect any underlying cause leading to amyloidosis was conducted, including whole-skeleton radiology and bone marrow examination, but no definite conclusion was reached. Although there was no history of recurrent painful crises or arthralgias, and her family history was negative, we decided to perform a molecular test for the detection of the more common pyrin mutations associated with FMF [1]. The patient was found to be doubly heterozygous for the M680I/M694V mutation, thus confirming the diagnosis of FMF. She began a daily regimen of colchicine prophylaxis (1.5 mg). The patient is currently under a regular follow-up, and to date, one year later, there is no further deterioration of her renal function.

Comment

This case of FMF represents the so-called phenotype II form of this disease. This form is totally asymptomatic, renal amyloidosis being a late presenting symptom. According to the literature it does not seem to be common in families with FMF cases, which raises important questions [2,3]. In this context, the patient described here deserves attention especially in a country that is believed to be free of this entity. As colchicine prophylaxis can effectively prevent disease progression, it is evident that in FMF phenotype II, a pre-symptomatic diagnosis is mandatory for applying prophylaxis early. Today, molecular detection enables the identification of affected individuals prior to the development of any symptom. Therefore, further testing for FMF mutations is recommended for any atypical presentation.

Despite a long-standing clinical belief of the rarity of the disease in Greece, there is recent evidence that the disease may not be as uncommon as previously thought [4]. Geographically and historically, Greece has been in close and long-lasting contact with other populations of the Mediterranean basin that are very rich in the FMF gene. It would appear therefore that in any case of renal AA amyloidosis, FMF should be excluded even if the patient does not apparently belong to a high risk group in terms of race or religion. This is further justified by the beneficial effects of colchicine treatment. Testing of other family members – even if not fully justified – may permit a better insight into the elusive topic of phenotype II FMF. Some authors propose that asymptomatic testing may allow pre-clinical diagnosis of FMF [5]. Furthermore, molecular testing of family members may lead to a better understanding of the geography of pyrin mutations and of the role of modifying gene(s) in FMF expression.

FMF = familial Mediterranean fever

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