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Diagnostic difficulties in chronic kidney disease – Is it or is it not Fabry disease?

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Abstract

Introduction. Renal impairment and neurological symptoms are common manifestations of Fabry disease. Although rare, Fabry disease should be taken into consideration when consulting a patient who presents with neurological and renal impairment, acroparesthesia and fatigue. The aim of this paper is to discuss the case of a female patient presenting with mild systemic symptoms and consequent renal impairment. Case report. The female patient, aged 64, presented for a painful ankle swelling, acroparesthesias, nycturia and fatigue. We diagnosed a gout attack, but found that she had biological signs of renal impairment, aggravated by the use of non-steroidian anti-inflammatory drugs. The search for an etiology of her renal failure proved difficult because she refused the kidney biopsy. The positivity of pANCA antibodies added another potential cause of kidney disease. The mild deficiency of alpha-galactosidase could not fully support the diagnosis of Fabry disease. Discussions and conclusions. In women, Fabry disease should be suspected even if the symptomatology is not typical and as severe as in men. It is difficult to diagnose the Fabry disease in a female patient with chronic kidney disease, because of its polymorphic manifestations and association with other comorbidities, in our case, pANCA vasculitis.

Keywords: Fabry disease, chronic kidney disease, vasculitis

Introduction. Fabry disease is a rare X-linked recessive genetic metabolic disorder [1], characterized by a deficiency of alpha-galactosidase A enzyme (also known as ceramide trihexosidase), which causes a pathological accumulation of globotriaosylceramides in the blood vessel walls of the entire body, predominantly in the skin, heart, kidneys and nervous system [1, 2, 3]. The disease is found in all ethnic groups and is more frequent in males, with an estimated incidence of 1:40 - 60,000 [2].

Unlike other diseases with X-linked inheritance, in the case of Fabry disease, women also have the classical manifestations of the disorder, including nervous system involvement, renal impairment, acroparesthesia or/and fatigue on exertion [4]. They also have a high risk of developing arterial hypertension, cardiac diseases, procoagulant status and renal failure. The disease progression is very slow, so that clinical manifestations related to this disease occur around the age of 30 -45 years [5].

Diagnosis is confirmed by demonstrating enzymatic deficiency in men and by identifying the specific ***GLA*** gene mutation in both genders. A special mention should be made in the case of potential female carriers of the genetic mutation, in whom the enzymatic activity level is at the lower normal limit and who require DNA analysis for a certain diagnosis [6].

Case report. Patient C.L., female, aged 64, from an urban area, with known *psoriasis vulgaris* and arterial hypertension stage III with moderate additional risk, presented for pain and functional impotence with tumefaction of the left internal malleolus, with onset about one month before. Aditionally, she presented nausea, nycturia, asthenia and fatigability, acroparesthesia in the lower limbs, symptoms having persisted for the past few months.

We mention that the patient had repeated episodes of superficial thrombophlebitis in the lower limbs during the last year (diagnosed in another medical service), and 2 months prior to the current admission, she experienced an episode of pulmonary thromboembolism documented by CT angiography, for which she was receiving oral anticoagulant treatment at admission. The patient was not investigated for antiphospholipid syndrome, thrombophilia or other causes that may induce hypercoagulability.

Clinical examination at admission showed an afebrile patient, with moderately altered general status, pale skin, blood pressure (BP) = 110/60

mmHg, respiratory rate (RR) = 83/minute, without detectable pathological changes of the cardiovascular or respiratory system. In the left internal malleolus, a swollen area of approximately 3 cm^2 was evidenced, with Celsian signs and partial limitation of motor function at this level.

Biologically, moderate microcytic hypochromic hyposideremic anemia (Hb = 8.8 g/dl, serum iron 36 microg/dl), marked inflammatory syndrome, nitrogen retention syndrome with a GFR = 16 ml/min/1.73m^2

were evidenced. Urinary analysis detected hematuria (250 RBC/field), proteinuria (15 mg/dl), and uroculture showed multi-resistant *E. coli* urinary infection, for which a single fosfomycin dose was administered according to the antibiogram.

Swelling and pain localized in the left internal malleolus were interpreted as local inflammatory reaction (more likely in the context of a gout attack, given the high serum uric acid value – 7.1 mg/dl), for which colchicine was administered according to protocols, which led to a spectacular improvement of malleolar changes, with the disappearance of pain and swelling, but renal function progressively deteriorated.

This was interpreted as recent kidney failure (we mention that there were no previous documents regarding renal function). Ultrasound detected normal size kidneys and hyperechoic parenchyma. No changes in the values of anti-MBG antibodies (Ab) were detected (physiological values), which is why the suspicion of vasculitis was raised and a diagnostic algorithm was initiated in this respect.

Immunological examinations: positive antinuclear antibodies ANA (1/320), positive pANCA antibodies (1/160), positive anti-MPO (pANCA) antibodies (195 UR/ml), negative cryoglobulins, negative anti-dsDNA Ab, negative anti-Sclero 70 Ab, negative infectious screening (including negative HBs Ag and HCV Ab, HIV test), normal circulating immune complexes, normal C3 and C4 complement fractions, negative anticardiolipin antibodies, ASLO, rheumatoid factor and IgA, IgG, IgM within normal limits directed the diagnosis towards pANCA positive vasculitis with moderate/severe renal and peripheral neurological impairment (Birmingham score 29) [7]. We mention the fact that based on the investigations performed, no pulmonary or other organ involvement was evidenced. Given pANCA positivity, the most probable diagnosis was microscopic polyangiitis or pauci-immune crescentic glomerulonephritis. Neurological symptoms (acroparesthesia) and thrombotic events could also be interpreted in the context of vasculitis [8, 9].

Kidney biopsy, a key element both for the diagnostic algorithm of renal impairment and the subsequent therapeutic approach, was delayed due to anticoagulant therapy (which could not be discontinued at that point) on the one hand, and because of the patient's categorical refusal to undergo this procedure, on the other hand.

In the absence of histopathological arguments, this patient diagnosed with CKD KDIGO stage G4Ax, with a suspicion of pANCA positive vasculitis, was administered methylprednisolone pulse therapy, 3 courses of 500 mg, followed by oral prednisone therapy 40 mg/day, equivalent to 0.5 mg/kg body weight/day, in a single dose in the morning, while therapy with cytotoxic drugs (cyclophosphamide, mycophenolate mofetil or azathioprine) was delayed in the absence of renal morphological arguments.

After 1 month of corticotherapy, renal function was relatively stationary (KDIGO G4Ax), with a decreasing titer of pANCA antibodies, being known that ANCA titer is useful for the monitoring of response to treatment and that its reappearance is an indicator of disease relapse [10]. Renal puncture biopsy was reevaluated, but given the significantly improved clinical state and immunological remission of the patient, as well as her refusal, biopsy was again not performed. Corticotherapy was continued (prednisone 30 mg/day in a single morning dose).

At this reevaluation, the patient was accompanied by her son, aged 31, who had been diagnosed about 8 months before with chronic kidney disease (proteinuria = 26 mg/24h, GFR = 42 ml/min/1.73m^2) of undetermined etiology (negative pANCA Ab, negative antinuclear Ab), and who complained of acroparesthesia in the lower limbs. The patient reported that during childhood, her son had had repeated episodes of purpuric rash in the lower limbs and the lower abdominal area, for which he had been hospitalized, but which could not be demonstrated by medical documents. Considering that the patient had another daughter,

who was healthy, the suspicion of renal impairment as part of an X-linked inherited syndrome was raised.

Taking into consideration the pathology of both the mother (procoagulability status, proteinuria, renal failure, hypertension) and the son (chronic kidney disease with onset in the third decade of life, with rapid progression, a history of abdominal purpura, persistent proteinuria, acroparesthesia of the lower limbs), the suspicion of Fabry disease was raised. It was decided to test the two subjects for Fabry disease; they both had a mild alpha-galactosidase deficiency, which was not significant to allow confirming Fabry disease.

Due to renal function impairment, the son was put on a waiting list for kidney transplantation, and the mother continued to receive corticotherapy for the next 8 months. During this period, the patient had non-sustained paroxysmal supraventricular rhythm disorders (supraventricular extrasystoles), relatively stationary, slightly improved renal function (KDIGO G3bAx), and a decreasing pANCA antibody titer, which was negative at about 1 year from the initiation of corticotherapy that was gradually reduced to a single morning prednisone dose of 15 mg/day.

Given that the mother's renal function was improving, the need for kidney biopsy was reconsidered (this was not considered appropriate for diagnostic accuracy alone, as it is an invasive procedure that involves certain risks). The prednisone dose was readjusted to 10 mg/day in a single morning dose, with a favorable clinical evolution. The patient's son was still on the waiting list for kidney transplantation.

Discussion. Conclusions. Anderson-Fabry disease (FD) is a rare lysosomal storage disease, currently having more than 800 pathogenic mutations in the ***GLA*** gene [11]. Recently, emphasis has been placed on understanding the clinical characteristics specific to a mutation, which might lead to a clinically relevant subclassification of FD into classic, non-classic, late onset or specific organ variants. Due to a significant variation of FD regarding clinical symptoms, there is a great interest in characterizing the impact of genotypes in order to understand and individualize therapy in addition to enzyme replacement therapy (ERT) [12].

During the disease evolution, the majority of patients develop kidney failure as well as cardiac or cerebrovascular diseases. The major causes of morbidity and mortality are usually attributed to renal impairment (proteinuria and progressive renal failure), cardiac involvement (hypertrophic cardiomyopathy) and cerebrovascular complications [13].

In the kidney, electron microscopy initially evidences an accumulation of Gb-3 in podocytes [14]. Progressive glomerular injury is associated with the increase of the mesangial space, evolving into segmental and global glomerulosclerosis. Nephropathy as part of Fabry disease is only associated with a moderate prevalence of hypertension, compared to other chronic renal diseases [15].

Although several Fabry disease cases with renal manifestations alone were reported in the 1990's, the concept of a Fabry disease variant which causes only renal symptoms without the classic symptoms has become widely accepted after the report of Nakao *et al.* in 2003 [16]. The authors demonstrated this renal form of Fabry disease among hemodialysis patients. Their internationally disseminated report was the key factor from which screening for Fabry disease started, thus determining an increase of the diagnosis rate [17].

The diagnosis of certainty is made based on genetic analysis, because the plasma activity of alpha-galactosidase A is normal in the majority of patients carrying the disease (heterozygotes), and after a rigorous clinical and paraclinical evaluation [18].

In our case, the onset of the disease was renal impairment, the first symptoms suggestive of Fabry disease developing at a late age. Enzymatic determinations, although at the lower limit of normal values, do not allow confirmation or exclusion of the diagnosis. The analysis of genetic mutations and renal puncture biopsy [19] are undeniable arguments in the diagnosis of FD.

The disease evolution is favorable under enzyme replacement therapy [20], while prognosis is infaust, with the appearance of severe cardiac and renal complications, in its absence [21]. These patients are recommended genetic counseling and prenatal diagnosis in the case of families at risk [22, 23].

Patients with Fabry disease are frequently diagnosed at a late stage because clinical

manifestations vary depending on organ involvement. Rigorous history taking including family inquiry and renal biopsy examination by electron microscopy are required for early diagnosis.

The early initiation of enzyme replacement therapy can limit progression and improve therapeutic results. An important aspect of this disease, which is little described in the literature, would be the alteration of quality of life, which deteriorates with the severity of the disease, and the therapeutic scheme that may cause multiple restrictions and the limitation of various daily activities [24].

The difficulties encountered in the diagnostic algorithm of this patient included the delay of renal puncture biopsy, because of anticoagulant therapy as well as the patient's refusal to undergo this procedure (initially for personal reasons, subsequently because her clinical state clearly improved and she did not understand the importance of this intervention). RPB would have been decisive in confirming or excluding the diagnosis of vasculitis, given the apparently limited renal location of the disease and the suspicion of Fabry disease. On the other hand, a serious deficiency that hindered a well-justified diagnosis was the lack of a thorough genomic analysis, an expensive investigation which could not be performed for financial reasons. Also, the fact that the patient was followed up in several medical services caused a delay in the diagnostic algorithm, as well as a more difficult corroboration of medical data.

We emphasize once more the diagnostic difficulties in case of patients with chronic kidney disease and also, the necessity of inter-disciplinary team work for correct and efficient diagnosis and therapy especially since patients are young adults with profound alteration of life quality.

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