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Genetics and environment: pathogenetic factors of vasculitis?

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To the editor: Etiopathogenesis of vasculitis is not fully understood, and environmental factors have been implicated in genetically predisposed individuals.[1,2] The histological renal expression of systemic vasculitis is a pauci-immune necrotizing glomerulonephritis (PNG).[3] Two cases of familial vasculitis in two brothers living in a rural environment are reported here.

CASE 1

A 63-year-old male, a shepherd living in a rural environment. He consulted in 1988 for an impaired general status, and laboratory tests revealed oliguric acute renal failure. Histological analysis of renal biopsy found a necrotizing vasculitis with extracapillary proliferative glomerulonephritis. The patient was treated with corticosteroids and oral cyclophosphamide. No renal function improvement occurred, and renal replacement therapy was required until the patient died in 2003.

CASE 2

A 72-year-old male, a farmer living in a rural environment. In April 2004 he complained of cough, expectoration, fatigue, and anorexia. His family history revealed that the patient reported as case 1 was his brother. His parents had died at an advanced age, and he had two sisters with type 2 diabetes mellitus, one of them with a history of pulmonary tuberculosis.

Based on his personal history, clinical signs, and renal function impairment, a renal biopsy was performed, which confirmed the presence of PNG in the setting of a systemic vasculitis associated to P-ANCA (positive anti-MPO, titer 442 U/mL).

DISCUSSION

Pauci-immune necrotizing glomerulonephritis with extracapillary proliferation is the renal pathological expression of systemic vasculitis. This group of diseases is characterized by inflammation of small and medium-sized blood vessels, and includes Wegener's granulomatosis (WG), microscopic polyangeitis (MPA), Churg-Strauss syndrome, or vasculitis limited to the kidney.[3]

Their etiopathogenesis is unknown. Occurrence of these diseases in several members of a same family has suggested that genetic factors could contribute to its occurrence.[1] We report two cases of PNG as a renal manifestation of systemic vasculitis in two brothers. In case 2, the disease started when the first patient had already died. The presence on the same disease in two brothers could support the genetic component in the etiopathogenesis of vasculitis.

Some researchers have attempted to find associations of vasculitis with HLA genes.[1] Recent studies found a positive association with HLA DR1, particularly in patients with WG, and negative associations with HLA DR3, particularly in Churg-Strauss granulomatosis and polyarteritis nodosa.[1,4] Our patient had the haplotype A1, B8 B35 Cw4 Cw7 DR3 and DR5 DQ2. Case 1 haplotype is unknown because the patient died before the second patient experienced the disease.

It has also been suggested that environmental factors could contribute to disease development in genetically predisposed individuals.[2] Patients reported here lived in a rural environment, and some environmental component may possibly have contributed to occurrence of the same disease in both patients.

In conclusion, these two cases of PNG as an expression of systemic vasculitis in two brothers living in a similar environment could support the suggested hypothesis of an influence of environmental factors on the etiopathogenesis of vasculitis in genetically predisposed individuals.

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Intracranyal hypertension as presentation of neurobrucellosis in a patient on hemodialysis

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To the editor: Brucellosis is a zoonosis with a high incidence rate in Spain, particularly in rural areas. While neurological involvement is uncommon, it has clinical significance due to the associated morbidity.

We report the case of a 29-year-old male born in Senegal with an unremarkable epidemiological history. His clinical history included arterial hypertension and chronic kidney disease (CKD) from an unknown cause on chronic hemodialysis for one year. Patient reported low grade fever and fatigue for the past 15 days. During hemodialysis, he expe-

rienced headache, lethargy, and projectile vomiting. Physical examination revealed sleepiness and flapping, temperature of 37.4 ºC, blood pressure of 180/120 mmHg, rhythmic heart sound with panfocal systolic murmur (III/VI), and unremarkable pulmonary auscultation and abdominal examination. Normal neurological examination, with no meningeal signs. Laboratory test results included: blood glucose 82 mg/dL, urea 158 mg/dL, creatinine 14.16 mg/dL, GOT 61 U/L, GPT, 279 U/L, LDH 864 U/L, GGT 298 U/L, CRP 42.9, hemoglobin 12.0 g/dL, WBCs 5.38 10(9)/L with normal differential, and platelet count 167 10(3)/L. All other laboratory parameters were within normal ranges. Ophthalmoscopy: right eye with normal disc and macula, nasal bleeding, and temporal superior arcade with cotton wool exudates; left eye with normal disc. Patient was diagnosed of grade III hypertensive retinopathy. No pathological findings were made in CT and MRI of the brain. Diagnosis of accelerated arterial hypertension led to start intravenous antihypertensive treatment that achieved optimal control of pressure values, but neurological symptoms persisted. Cerebrospinal fluid (CSF) pressure was increased to 33 mg (normal, up to 20 mmHg), with leukocytosis (36 WBCs/mm^3) with a predominance of lymphocytes (70%), increased protein levels (87 g/dL), and low glucose (84 mg/dL). Serologic testing was positive for *Brucella*, Bengal rose, agglutination with anti-brucella antibodies 1/160, and immune capture with anti-brucella antibodies > 1/5120. CSF and blood cultures were positive for *Brucella spp.* Neurobrucellosis was diagnosed, and specific antibiotic therapy was started with doxycycline, rifampin, and trimethoprim-sulfamethoxazole. After five days of treatment, patient experienced a clear improvement, showing no fever or symptoms.

Incidence of brucellosis in Europe is low. In Spain, however, brucellosis is the main zoonosis, and endemic areas continue to exist, particularly in rural cattle-raising areas.[1] Clinical signs of brucellosis are very diverse, and genitourinary, gastrointestinal, and cardiological manifestations are most common. Central nervous system involvement by brucellosis (neurobrucellosis) is uncommon and mainly causes meningeal signs, although papilledema, optic neuropathy, radiculitis, and stroke may also occur.[2,3] Cases of neurobrucellosis have been reported in patients with CKD living in endemic areas.[4] In our patient, the condition occurred as intracranial hypertension and fever.

Diagnosis of neurobrucellosis should be considered in a patient with CKD who also has fever of unknown origin and neurological signs. When the disease is suspected based on clinical signs, serologic tests allow for confirming diagnosis, and germ isolation from culture is an even more definitive evidence, as in the reported case. While this is an uncommon condition, it should be kept in mind because early diagnosis and treatment decrease the high mortality associated to neurobrucellosis. Long-term treatment should be administered with two or three antibiotics able to cross the blood-brain barrier. Our patient received treatment for three months and has no neurological sequelae.

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Hypokalemia, distal renal tubular acidosis, and Hashimoto's thyroiditis

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To the editor: Renal tubular acidosis (RTA) is defined as the inability of renal tubule to acidify urine regardless of any reduction in glomerular filtration rate. Type I or distal RTA is a subtype characterized by an impaired hydrogen ion (H^+) secretion in the distal convoluted tubule. This defect may be inherited or acquired, and causes H^+ retention, with the resultant decrease in plasma bicarbonate and alkaline urine.[1,2] Most common cause of RTA I include diabetes mellitus, Sjögren's syndrome, multiple myeloma, primary amyloidosis, sarcoidosis, kidney transplant, obstructive uropathy, sickle cell disease, calcium metabolism disorders, and certain drugs.[1,2]

Thyroid hormone increases membrane cell Na^+, K^+-ATPase pumps.[3] In hypothyroidism, content and function of these pumps are reduced, which causes a decreased elimination of H^+, exacerbating the acidotic state caused by RTA. Hypocalcemia in hypothyroid patients is caused by type I RTA.[3-6]

Two patients with hypocalcemia due to renal tubular acidosis secondary to Hashimoto's thyroiditis are reported below. We suggest that this association is mediated by autoimmune mechanisms.

PATIENT 1

A 29-year-old female patient with progressive muscle weakness and quadriplegia, hyperchloremic metabolic acidosis with normal anion gap, and severe hypokalemia, which was corrected with intravenous potassium with clinical improvement. RTA type I, with high titers of anti-peroxidase antibodies (100 U/mL) and > 100 mU/mL of thyroid-stimulating hormone (TSH), was diagnosed. Despite adequate alkali administration, acid-base status was corrected when thyroid function was normalized. After treatment with levothyroxin and potassium citrate, the patient has been asymptomatic for the past 8 years.

PATIENT 2

A 30-year-old female patient with growth retardation due to type I RTA diagnosed in adolescence was admitted to hospital for a spontaneous hip fracture. Patient reported marked fatigue, weakness (quadriparesis), and muscle cramps for the past two years. Labora-