Netherlands
The Journal of Medicine

PHOTO QUIZ

The zebra among horses: extensive abnormalities in a kidney biopsy without clinical signs of kidney disease

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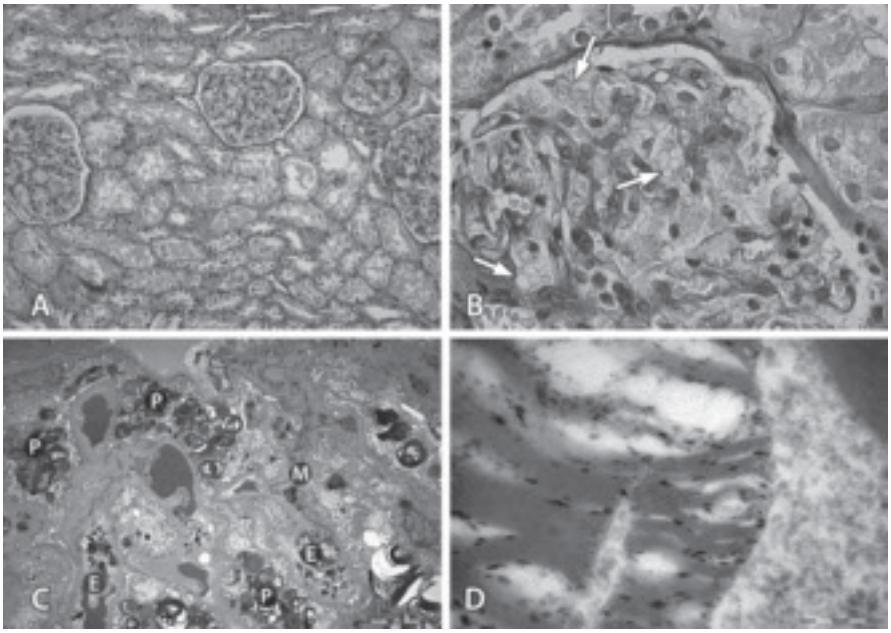
A 13-year-old boy presented to the outpatient clinic with a 4-5 year history of cramping pains in the hands and feet. The reported pains were so severe as to force him to lie down and, on occasions, vomit. The pains were intermittent in nature and more common during warm weather and on physical exertion. The patient was well apart from a history of migraines and a period of macroscopic haematuria diagnosed as post-streptococcal glomerulonephritis five years ago. Physical examination revealed some angiokeratomas on the face, thorax and arms. Blood pressure was 112/80 mmHg. Urinalysis (dipstick) was negative, no proteinuria was present (albuminuria < 3 mg/day) and kidney function was normal (serum creatinine 48 μmol/l, estimated glomerular filtration rate 128 ml/min/1.73m^2 (Schwartz formula)). Based on a Google search, the boy's parents suspected Fabry's disease. Cardiac ultrasound, MR brain and audiology testing were normal. Ophthalmoscopy revealed cornea verticillata. A kidney biopsy was performed.

WHAT IS YOUR DIAGNOSIS?

See page 335 for the answer of this photo quiz.

Figure 1. *A) Low magnification of the periodic acid Schiff staining showing no overt pathological changes, magnification x 10; B) High magnification of the periodic acid Schiff staining showing extensive vacuolisation of the podocytes (arrow), magnification x 40; C) Electron microscopy of one glomerulus showing lamellar structures in the cytoplasm of podocytes (P), endothelial cells (E), and mesangial cells (M); D) Electron microscopy at high magnification showing classical zebra bodies*



ANSWER TO PHOTO QUIZ (PAGE 331)

THE ZEBRA AMONG HORSES: EXTENSIVE ABNORMALITIES IN A KIDNEY BIOPSY WITHOUT CLINICAL SIGNS OF KIDNEY DISEASE

DIAGNOSIS

The kidney biopsy contained over 30 glomeruli without overt pathological changes at low magnification (*figure 1A*). At higher magnification, podocytes showed extensive but aspecific vacuolisation (*figure 1B*). Immunofluorescence was negative. At electron microscopy, massive accumulation of lamellated structures was present, not only in podocytes but also in endothelial cells, mesangial cells, parietal epithelial cells, fibroblasts and tubular epithelial cells (*figure 1C*). At higher magnification, 'zebra bodies' were seen (*figure 1D*) classical for Fabry's disease, an X-linked inborn error of the glycosphingolipid metabolic pathway. An alternative diagnosis would be renal phospholipidosis due to amphiphilic drugs (e.g. (hydroxy) chloroquine, amiodarone, gentamycin). The diagnosis was confirmed by mutational analysis and enzymatic testing of the leukocyte hydrolase alpha-galactosidase A (alpha-GalA) activity (< 0.5 nmol/h/mg protein (reference range 15-45)).

The clinical features of Fabry's disease result from lysosomal accumulation of globotriaosylceramide in a wide variety of cells. Neuropathic pains, predominantly in the limbs and precipitated by stress, extremes of heat or cold and physical exertion are characteristic for Fabry's disease and occur from a mean age of 10 years. Other symptoms of the disease tend to develop in the third and fourth decade and are rather nonspecific. These include telangiectasias and angiokeratomas, cardiac involvement (concentric left ventricular hypertrophy, heart failure), exercise intolerance, lymphadenopathy and gastrointestinal symptoms such as diarrhoea and abdominal pain. In view of the rarity of the disease, it is therefore understandable that a delay in diagnosis is common.[1]

Our patient did not have any of the renal symptoms reported in Fabry's disease (proteinuria, isosthenuria, Fanconi syndrome, decreased glomerular filtration rate or hypertension). Chronic kidney failure is common among untreated patients.[2] Affected males with very low levels of alpha-GalA activity, like our patient, tend to develop kidney failure from an earlier age.[2] Enzyme replacement therapy is reported to protect against progressive kidney function decline, and this might particularly be true when treatment is started early in the course of the disease.[3] For this reason a kidney biopsy was obtained despite the lack of renal symptoms. This case demonstrates that extensive kidney involvement of Fabry's disease might be present prior to clinical signs of kidney damage, e.g. microalbuminuria or decreased glomerular filtration rate.

REFERENCES

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