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FABRIJEVA BOLEST: DIJAGNOSTIČKI LABORATORISKI PROTOKOL

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Kratak sadržaj: Fabrijevo oboljenje je nasledna sfingolipidoza uzrokovana mutacijom gena na X-hromozomu koji je odgovoran za ekspresiju lizozomalne hidrolaze, α-galaktozidaze A (α-gal; EC 3.2.1.22). Nedostatak enzima rezultira u akumulaciji nerastvornih glikosfingolipida u lizozomima endotelijalnih, peritelijalnih i ćelijama glatkih mišića krvnih sudova. Glavni klinički znaci u obolelih klasičnih homozigota koji nemaju α-gal su kožne lezije (angiokeratomi), oftalmološke promene (kornealna distrofija), neurološke promene, kardiovaskularna i renalna oboljenja. U homozigotnih muškaraca prognoza je vrlo loša, smrt se dešava uglavnom u petoj deceniji života uglavnom zbog renalne insuficijencije ili srčanog infarkta. Klinički tok i prognoza Fabrijeve bolesti u heterozigotnih žena je blaža u najviše slučajeva, mada neke žene mogu da obole zbog X-hromozomske inaktivacije. Dijagnostika homozigota se obezbedjuje rutinskim dokazivanjem smanjenja aktivnosti α-gal u serumu, perifernim leukocitima ili kulturi fibroblasta a potom potvrdjuje genetskom analizom. Genotipizacija je esencijalna metoda za potvrdu biohemijskih rezultata i genetsko savetovanje porodice ali ne i za primarno dijagnostiku pacijenata. Ovde je predstavljen slučaj homozigotnog muškarca, starog 19 godina, sa dijagnozom Fabrijeve bolesti od pre dve godina, na osnovu prisutnih angiokeratoznih promena naročito izraženih na nogama i butinama i blagom kornealnom distrofijom. Neuropsihološka, kardiološka i nefrološka ispitivanja su bila negativna. Odredjivanjem koncentracije aktivnosti leukocitne α-gal sa fluorescentnim supstratom je dokazan nedostatak aktivnosti α-gal (0,7 nmol/h/mg proteina; normalan opseg: 60 137), što je potvrdilo kliničku sumnju. Laboratorijskim analizama je utvrdjena proteinurija (1,35 g/L; normalane vrednosti manje od 0,15 g/L). Majka pacijenta je imala sniženu vrednost aktivnosti α-gal (30 nmol/h/mg proteina). Genetske analize su u toku. Vrlo je važno na vreme dijagnostikovati pacijente sa Fabrijevim obolenjem, kako zbog davanja adekvatne terapije tako i zbog otkrivanja ženskih nosioca Fabrijeve bolesti i genetskog savetovanja.

Ključne reči: Fabrijeva bolest, α-galaktozidaza A, homozigot, periferni leukociti, fluorescentni supstrat

FABRY'S DISEASE: DIAGNOSTIC LABORATORY PROTOCOL

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Summary: Fabry's disease is a sex-linked inherited sphyngolipid storage disorder caused by mutations within the gene responsible for the expresion of the lysosomal hydrolase, α-galactosidase A (α-gal; EC 3.2.1.22). The enzyme defect results in the progressive deposition of uncleaved glycosphingolipids within lysosomes of endothelial, perithelial and smooth muscle cells of blood vessels. The major clinical features in classically affected homozygotes who have no detectable α-gal may be divided into cutaneous lesions (angiokeratoma), ophthalmological abnormalities (corneal dystrophy), neurological abnormalities, cardiovascular diseases, and renal involvement. In homozygous men prognosis is poor, death occurs generally within the 5th decade of life mainly because of renal insufficiency or cardiac stroke. The clinical course and prognosis of Fabry's disease in heterozygous women is considered mild in most cases, although some females may be severely affected as a result of non-random X inactivation. The diagnosis is routinely achieved in homozygote patients by proving a severe reduction of α-gal activity in serum, peripheral leucocytes or cultured fibroblasts and then confirmed by gene analysis. Genotyping is the essential method for confirmation of biochemical results and for genetic counseling but not for the primary detection of patients. We present a young homozygous male, 19 years old, diagnosed as affected by pre-symptomatic Fabry's disease two years ago. He presented angiokeratomas particularly diffused at the legs and buttocks and mild corneal dystrophy. Neuropsyhological, cardiological and nephrological evalutions were negative. Concentrations of leukocytes α-gal activity were determined, using a fluorescence substrate and a documented deficiency of α-gal activity (0.7 nmol/h/mg protein; normal rage: 60 137), confirmed clinical suspect. The laboratory examinations, revealed a renal involvment, characterized by mild proteinuria (1.35 g/L with a normal level lower than 0.15). Patient's mother, a 50-year old women, had a residual leukocyte α-gal activity of 30 nmol/h/mg protein. Molecular genetic examinations are in process. It is very important to recognize the patients with Fabry's disease on time in order to treat them properly and also to identify the female carriers of Fabry's disease for the right genetic counselling.

Key words: Fabry's disease; α-galactosidase A; homozygote; peripheral leukocytes; fluorescence substrate