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ORIGINAL ARTICLE

Screening for Fabry Disease in Patients With Juvenile Systemic Lupus Erythematosus

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ABSTRACT

Objectives: This study aims to determine the prevalence of Fabry disease (FD) among patients with juvenile systemic lupus erythematosus (SLE).

Patients and methods: This cross-sectional study included 76 juvenile SLE patients (12 males; 64 females; mean age 16±3.3 years; range, 8 to 23.5 years) who were diagnosed according to 1997 update of the 1982 American College of Rheumatology revised criteria for classification of SLE. Since the majority of patients were female, alpha-galactosidase A gene was investigated for mutations resulting in FD. Lysosomal accumulation of globotriaosylsphingosine (lyso-Gb3) was further evaluated in mutation positive subjects by using dried blood spot testing.

Results: Alpha-galactosidase A gene screening did not yield any positive mutation in our 74 subjects. However, a heterozygous p.D313Y mutation was found in two females. These subjects were further investigated for lyso-Gb3 levels in dried blood spot samples and the levels of lyso-Gb3 being normal lead to exclusion of FD in these two patients.

Conclusion: We do not suggest routine screening of FD in patients with juvenile SLE; however, prospective studies with larger sample sizes are needed for further analysis.

Keywords: D313Y mutation, Fabry disease, genetic screening, juvenile systemic lupus erythematosus.

Fabry disease (FD) is an X-linked lysosomal storage disorder (LSD), which demonstrates similar organ involvement patterns with systemic lupus erythematosus (SLE).[1,2] Besides cutaneous and musculoskeletal manifestations, renal and neurologic involvement could be seen in the course of both diseases.[1,2-12] Deficient activity of lysosomal alpha-galactosidase enzyme that is caused by mutations in alpha-galactosidase A (GLA) gene is responsible for clinical manifestations. The lack of enzyme activity results in the progressive accumulation of neutral glycosphingolipids, primarily globotriaosylceramide (Gb3), within lysosomes in a variety of cell types, including endothelial, renal, cardiac and nerve cells.[1,13] First symptoms typically arise from childhood or adolescence including peripheral pain, hypohidrosis, cornea verticillata and gastrointestinal symptoms such as abdominal pain, diarrhea and food intolerance. Signs and symptoms that tend to develop later in adulthood are associated with end-organ failure and premature death. These include progressive renal insufficiency, cardiac hypertrophy and

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arrhythmia, other cardiovascular disease and early stroke.[1,13-17] Although FD has traditionally been considered as an X-linked recessive disorder, currently it is classified under the group of X-linked diseases due to the presence of clinical manifestations in females. A more quiescent and nonspecific disease course is encountered particularly in females and children. Hence, delay in diagnosis and treatment is frequently observed in these groups.[14-17]

Lysosomal storage disorders are characterized by excess storage of undigested or partially digested materials within the lysosomes of affected cells and many studies pointed out that the entire clinical picture does not correlate with the degree of storage. Different studies have already shown the involvement of inflammatory processes and immunopathologic associations in various sphingolipidoses.[18-20] In addition, autoantibodies may play an important role in the pathogenesis of GM2 gangliosidoses.[20] The co-existence of FD and various immune disorders such as SLE, rheumatoid arthritis, juvenile idiopathic arthritis and immunoglobulin A nephropathy have already been reported.[2-6,21,22] Furthermore, rheumatic diseases misdiagnosed as FD were also reported.[13]

Presence of SLE associated autoantibodies in FD and co-occurrence of FD and SLE have been previously reported in isolated case reports.[2-7] However, to our knowledge, a systematic screening of FD in juvenile SLE has not been performed up to date. In this study, we aimed to determine the prevalence of FD among patients with juvenile SLE.

PATIENTS AND METHODS

This cross-sectional study was conducted at the outpatient pediatric rheumatology clinic of Istanbul University Cerrahpasa Medical Faculty between January 2016 and June 2016 and included 76 juvenile SLE patients (12 males; 64 females; mean age 16±3.3 years; range, 8 to 23.5 years). Diagnosis of all patients was confirmed by a pediatric rheumatologist according to the 1997 revised criteria of American College of Rheumatology for classification of SLE.[23] The study protocol was approved by the Istanbul University Cerrahpasa Medical Faculty Ethics Committee (29/09/2015-346002). A written informed consent was obtained from alll patients or their parents. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were also evaluated by a pediatric metabolic disease specialist and symptoms of FD such as hypohidrosis, burning pain in extremities, tinnitus, hearing loss and gastrointestinal symptoms were investigated. Physical examination for angiokeratomas and ocular examination for cornea verticillata were performed. Family history of kidney disease, premature stroke and cardiomyopathy were noted.

Since the majority of the patients were female, molecular genetic testing to identify GLA mutations was performed initially. GLA gene sequence analysis was performed by using the MiSeq next generation sequencing platform (Illumina Inc., San Diego, CA, USA), a Food and Drug Administration-approved diagnostic system. All coding exons of the gene and their flanking splice site junctions were amplified using polymerase chain reaction primers, designed with PRIMER©-Primer Designer version 2.0 software (Scientific & Educational Software programme: Denver, CO, USA). Libraries were prepared with the Nextera XT kit (Illumina Inc., San Diego, CA, USA), according to the manufacturer's instructions. Next-gene sequencing was carried on MiSeq (Illumina Inc., San Diego, CA, USA). Sequences were aligned to the hg19 genome within MiSeq Reporter software (Illumina Inc., San Diego, CA, USA). Visualization of the data was performed with IGV 2.3 software (Broad Institute: Cambridge, MA, USA). Plasma globotriaosylsphingosine (lyso-Gb3) was further analyzed in mutation positive subjects by using dried blood spot testing.

RESULTS

The mean duration of the course of disease was 4.4±2.9 years (Table 1). The most prevalent clinical features in our cohort were mucocutaneous manifestations (97.4%), followed by hematological (61.8%) and musculoskeletal manifestations (56.6%). Renal involvement was present in 23 patients (30.3%). Among 20 patients who underwent kidney biopsy, 14 were classified

Table 1. Demographic and clinical characteristics together with laboratory assessment of patients with juvenile systemic lupus erythematosus (n=76)

Demographic features	n	%	Mean±SD
Age (year)			16.0±3.3
Age at disease onset (year)			11.6±3.6
Age at diagnosis (year)			12.3±3.4
Sex			
Female		84.2	
Male		15.8	
Mean disease duration (year)			4.4±2.9
Constitutional manifestations	43	56.6	
Fever	29	38.2	
Fatigue	33	43.4	
Anorexia	32	42.1	
Weight loss	21	27.6	
Arthralgia	45	59.2	
Mucocutaneous involvement	74	97.4	
Malar rash	58	76.3	
Discoid rash	10	13.1	
Photosensitivity	34	44.7	
Alopecia	6	7.8	
Oral lesions	46	60.5	
Hematological involvement	47	61.8	
Musculoskeletal involvement	43	56.6	
Arthritis	41	53.9	
Myositis	4	5.3	
Renal involvement	23	30.3	
Hypertension	13	17.1	
Pulmonary hypertension	2	2.6	
Neuropsychiatric involvement	11	14.5	
Serositis	10	13.2	
Cardiac involvement	2	2.6	
Antiphospholipid antibody syndrome	3	3.9	
Antinuclear antibody positivity	73	96	
Anti-dsDNA positivity	63	82.9	
Anticardiolipin antibody positivity	9	11.8	
Low complement levels	45	59.2	

SD: Standard deviation; Anti-dsDNA: Anti-double stranded deoxyribonucleic acid.

as class III-IV, five as class II and one as class V based on histopathological analysis. Antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid were positive in 96% (n=73) and 82.9% of the patients (n=63), respectively. Parental consanguinity was present in 25% (n=19) of the patients. Fourteen patients had reported burning sensation in hands and feet; two patients had hypohidrosis and 11 patients had gastrointestinal complaints. Neither cornea verticillata nor angiokeratoma was detected in any of the patients. GLA gene screening did not yield any positive mutation in 76 patients. However, a heterozygous p.D313Y was found in two female patients. These patients were further investigated for globotriaosylsphingosine (lyso-Gb3) levels in dried blood spot samples and the levels of lyso-Gb3 being normal led to exclusion of FD in these two patients.

DISCUSSION

The number of clinicians and researchers interested in LSDs, particularly in FD, has been increasing, depending on the options available to expand the diagnosis and treatment. Because of the cryptic symptoms and rarity of FD,

the diagnosis of patients is often delayed and manifestations of FD are usually attributed to other diseases.[13,14,17,24] Therefore, screening studies in high-risk groups for FD have been performed, including patients with idiopathic kidney failure, hypertrophic cardiomyopathy and premature stroke.[25-27]

The pathogenesis of LSDs is rather still a mystery. Besides storage inflammation, oxidative stress and immunologic aspects have been thought to be effective in progression of the disease.[18-20,28-30] A recent study showed high ANA titres in FD patients, which is a sensitive autoantibody in the diagnosis of SLE.[7] Moreover, FD may pose diagnostic dilemma in some circumstances; differentiation from rheumatic diseases may occasionally be difficult.

In this study, we aimed to investigate if there is an association between FD and SLE. Misdiagnosis of FD is common in heterozygous females because of the borderline enzyme levels and females are not usually clinically evaluated unless they present with serious complications of FD. For this reason, GLA mutation analysis for screening of FD was preferred in our juvenile SLE cohort, in which females were predominant (84.2%). Another useful method for diagnosis of FD is detection of lyso-Gb3 levels, which indicates lysosomal accumulation of Gb3.[31] In our study, only two of 76 patients were found to carry heterozygous p.D313Y mutation, which was reported as a non-pathogenic variant in recent studies.[32,33] Lyso-Gb3 levels were within normal ranges in patients with positive p.D313Y mutation; therefore, FD was excluded.

Enzyme replacement therapy is the most effective management option in FD patients without signs and symptoms of organ involvement.[14,29] Screening female patients in group of disorders which have similar clinical findings with FD is important. Screening for FD has recently been implemented in newborn screening programs in an increasing number of countries.[34,35] In countries without a newborn screening program for FD, the most important question to be answered is which patients or patient groups should be screened for FD. Several studies have recommended screening FD in patients on hemodialysis, in cases of premature cryptogenic stroke and in all cases of unexplained hypertrophic cardiomyopathy.[26-28] A recent study has also suggested that screening of FD in rheumatic diseases may be beneficial.[36]

The limitation of our study is the relatively small sample size since juvenile SLE and FD are both rare disorders.

In conclusion, coexistence of SLE and FD has been reported in case reports previously; however, to our knowledge, a systematic screening of juvenile SLE for FD has not been performed. We have not detected any FD in our juvenile SLE cohort. Thus, we do not suggest routine screening of FD in patients with juvenile SLE. However, future prospective studies with larger sample sizes are needed to clarify our findings.

Declaration of conflicting interests

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