Coexistence of Fabry Disease and Antiphospholipid Syndrome: A Prospective Cohort Study

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ABSTRACT **Background:** Antiphospholipid syndrome (APS) is a common form of acquired thrombophilia associated with a high thrombotic risk. Fabry disease (FD) is an X-linked lysosomal storage disease caused by mutations in the alpha-galactosidase A (*GLA*) gene and presents with a wide range of clinical manifestations, including a high rate of thrombosis. Previously reported, 45% of FD patients were found to have antiphospholipid autoantibodies.

Objectives: To determine the prevalence of FD in patients with APS.

Methods: We conducted a prospective study. Data were collected from 41 APS patients at our outpatient clinic at Meir Medical Center in Israel. We utilized chemical and genetic analyses to identify FD among APS patients. Dried blood spot (DBS) was used to assess GLA activity in males, and mutational analysis of the GLA gene was performed by sequencing exons and their flanking regions in women.

Results: Among 41 antiphospholipid patients, one male patient was diagnosed with FD. Gal variants were not detected in any of the tested female patients.

Conclusions: We found a low prevalence (2.4%) of FD in APS patients. Larger studies are needed to evaluate the clinical utility and cost-effectiveness of routine FD screening in this population.

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KEY WORDS: alpha-galactosidase A (GLA), antiphospholipid syndrome (APS), Fabry disease

Fabry disease (FD) is a rare, X-linked lysosomal storage disorder caused by mutations in the alpha-galactosidase A (*GLA*) gene, which encodes α-galactosidase A (α-Gal A). This enzyme deficiency leads to the accumulation of globotriaosylceramide (Gb3) in various tissues, including blood vessels, skin, kidneys, eyes, and the central and peripheral nervous systems [1]. Patients may exhibit multiple clinical phenotypes, such as cardiovascular disease, neuropathic pain, thrombotic events, gastrointestinal manifestations, kidney involvement, and even risk of early death. [2-4]. Approximately 15% of FD patients present with a hypercoagulable state, increasing their susceptibility to thrombotic events and vascular complications [5]. APS is a thrombo-inflammatory disease propelled by circulating autoantibodies that recognize cell surface phospholipids and phospholipid binding proteins. The result is an increased risk of thrombotic events, pregnancy morbidity, and various other autoimmune and inflammatory complications [6].

The 2023 American College of Rheumatology and the European Alliance of Associations for Rheumatology classification for antiphospholipid syndrome (APS) involve clinical and laboratory criteria. Clinical criteria include one episode of vascular thrombosis or pregnancy morbidity (unexplained fetal death after 10 weeks, premature birth due to severe preeclampsia or placental insufficiency, or three consecutive miscarriages before 10 weeks). Laboratory criteria require positive antiphospholipid antibodies on two or more occasions, such as lupus anticoagulant or anticardiolipin antibodies (IgG/IgM), with tests conducted at least 12 weeks apart. Diagnosis of APS requires at least one clinical and one laboratory criterion. [7].

Considering previous study from 2007, which indicated that 45% of FD patients possess antiphospholipid autoantibodies [8], we investigated the prevalence of FD among patients diagnosed with APS at our clinic. We hypothesized that we would identify cases of FD within this population. We sought to determine the prevalence of FD among APS patients as well to explore the potential for these individuals to benefit from treatment, particularly through enzyme replacement therapy (ERT), which can prevent serious complications associated with FD [9].

PATIENTS AND METHODS

This prospective cohort study included adult patients diagnosed APS at Meir Medical Center, Israel, from December 2018 to June 2019. The study was approved by the Meir Medical Center Ethics Committee (protocol number: 0255-17-MMC, NCT03384485), with written informed consent obtained from all participants. Each underwent a clinical examination and provided a blood sample for FD testing.

The inclusion criteria included age older than 18 years, diagnosis of APS, fand ollowed at Meir Medical Center. Those unable to provice informed consent were excluded from the study population.

TESTING FOR FD

DBS samples were collected via finger prick and sent to Archimed Life Science GmbH Laboratories (Vienna, Austria). In males, α-galactosidase A (α-Gal A) activity was measured, with values below 1.2 µmol/L/h indicating FD. In females, *GLA* gene sequencing was conducted, as they may present partial or complete α-Gal A deficiency. For borderline results, further genetic and enzymatic testing, including lyso-Gb3 measurement, was performed.

RESULTS

A total of 41 patients participated; 26 females (63.41%) and 15 males (36.59%), with a mean age of 43.02 ± 12.2 years. Notable co-morbidities included smoking (31.71%), type 2 diabetes mellitus (24.39%), hyperlipidemia (39.02%), chronic renal failure (4.88%), and hypertrophic cardiomyopathy (2.44%). Common clinical manifestations in the cohort were deep vein thrombosis (DVT), miscarriages, and transient ischemic attack, which are consistent with APS complications [Table 1]. Genetic testing for FD was performed on all 41 patients. All females had negative *GLA* gene sequencing results, excluding FD. Among the males, 12 exhibited high α-Gal A enzyme activity, precluding FD. Two males with borderline α-Gal A activity underwent *GLA* gene sequencing. The results were negative, excluding FD in these cases. One male had low α-Gal A activity, confirmed by positive *GLA* gene sequencing, establishing a diagnosis of FD. Statistical analysis found no significant associations between APS manifestations and FD. Overall, the prevalence of FD in this cohort was 2.4%.

An unexpected diagnosis of FD emerged during the evaluation of a 57-year-old male with APS, a history of DVT managed with long-term anticoagulation, a 35 pack-year smoking history, and well-controlled type 2

Table 1. Demographic, clinical, and Fabry disease screening results of antiphospholipid syndrome patients

Variable	Category	Frequency (N)	Percentage (%)
Sex	Female	26	63.41%
	Male	15	36.59%
Co-morbidities	Smoker	13	31.71%
	Diabetes mellitus type 2	10	24.39%
	Hyperlipidemia	16	39.02%
	Chronic renal failure	2	4.88%
	Hypertrophic cardiomyopathy	1	2.44%
Clinical manifestations	Deep vein thrombosis	12	29.3%
	Miscarriage	9	22.0%
	Transient ischemic attack	5	12.2%
	Cerebrovascular accident	4	9.7%
	Pulmonary embolism	2	4.8%
	Thrombocytopenia	4	9.7%
Fabry disease screening results	Confirmed Fabry disease	1	2.4%
	Borderline result	2	4.9%
	Negative result	38	92.7%

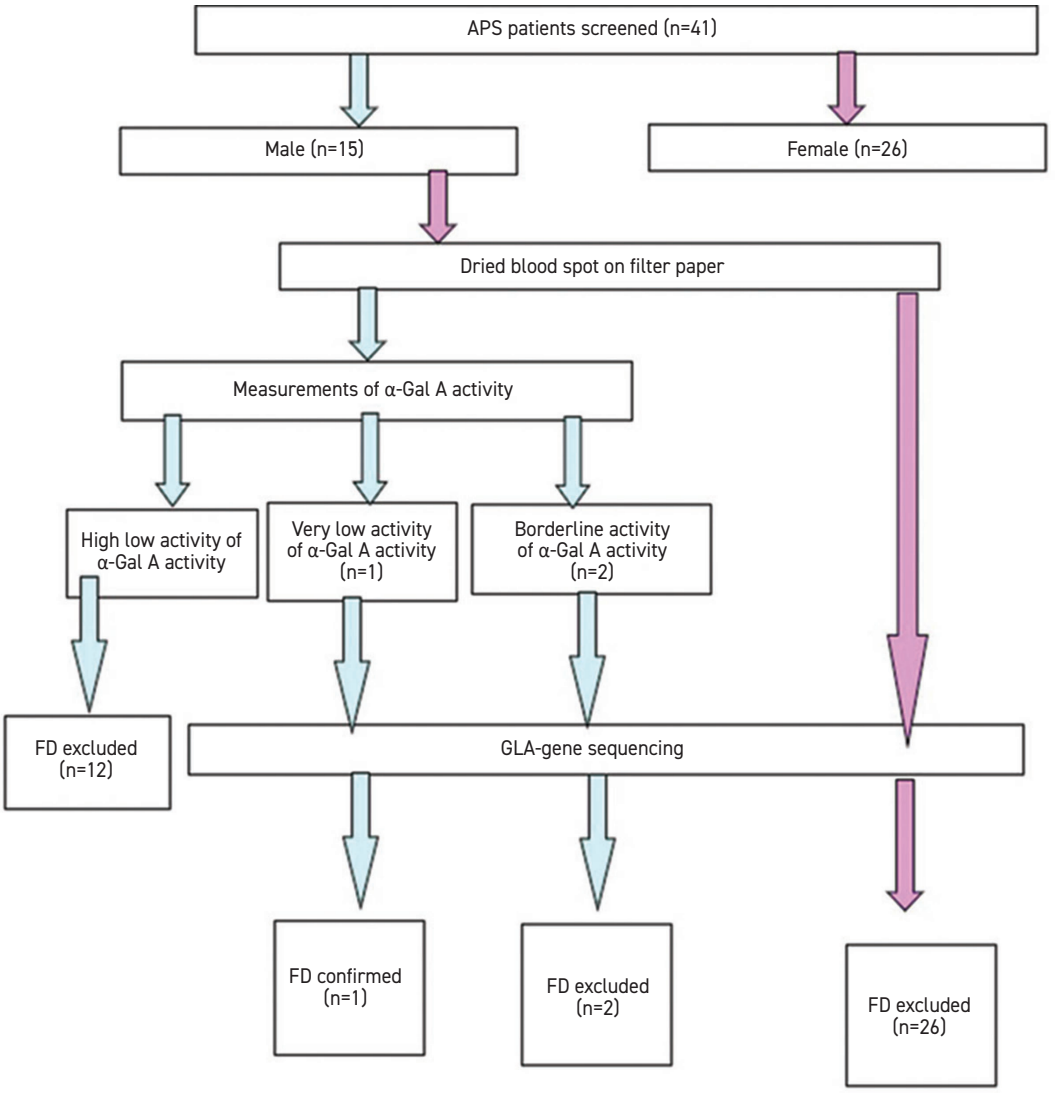
diabetes mellitus (10 years, controlled with metformin). He presented for evaluation of proteinuria. While asymptomatic on physical examination except for mild bilateral lower extremity edema, laboratory findings revealed significant proteinuria (2.0 g/24 hours). Renal function was preserved (serum creatinine 1.1 mg/dl, eGFR 75 ml/min/1.73 m², HbA1c 7.6%). Echocardiography showed a normal left ventricular ejection fraction, ruling out heart failure as the cause of edema. Given the proteinuria, angiotensin-converting enzyme inhibitors were initiated, and the patient was referred for genetic counseling and consideration of enzyme replacement therapy [Figure 1].

DISCUSSION

Information regarding the prevalence of FD among patients with APS is sparse, with few studies addressing the coexistence of systemic autoimmunity and FD. Previous studies have highlighted that FD coexists with other autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Moreover, a direct

Figure 1. Flowchart of FD screening and diagnostic process in APS patients

α-Gal A = α-galactosidase A, APS = antiphospholipid syndrome, FD = Fabry disease, GLA = alpha-galactosidase A



association between FD and APS has been suggested, as indicated by a case report detailing an SLE patient with both FD and APS [10-13]. Koca and colleagues [14] demonstrated an incidence of 11.7% for anticardiolipin antibodies among patients with FD. In addition, Martinez and co-authors [8] found that antiphospholipid autoantibodies were present in 45% of their cohort (15 of 33 patients), with a notably high prevalence of 12% for anticardiolipin autoantibodies. This high rate of thrombosis associated with FD may partly stem from the presence of these antiphospholipid autoantibodies, underscoring the necessity for clinical correlation to identify any underlying autoimmune diseases. This finding, while seemingly at odds with previous observations of a high rate of antiphospholipid antibodies in FD patients, is also explained by the inherent rarity of FD itself. The prevalence of FD is estimated to be between 1 in 40,000 and 1 in 120,000 individuals [15]. Consequently, the observed low prevalence in our APS cohort is not unexpected, even if a correlation exists. This result highlights the challenges in detecting a relatively rare disease within a specific population, underscoring the need for larger studies to definitively assess the association between APS and FD. The clinical overlap between FD and APS is particularly significant regarding thrombotic events. The severity of these thrombotic complications highlights the urgent need for early diagnosis and intervention. Timely detection is essential for the effective management of FD. Numerous studies have established the safety and efficacy of recombinant α-Gal A replacement therapy (ERT), demonstrating its potential to prevent recurrent thrombotic events, especially when initiated at an early stage [5,8].

Nevertheless, physicians treating APS patients should remain mindful of the key features of FD, including thrombotic events, to consider this diagnosis during the etiological assessment. This awareness is crucial for reducing the classic wandering time often observed in FD diagnosis and for offering specific treatments that effectively prevent recurrent thrombotic events. Timely interventions are vital for improving the long-term outcomes and quality of life for individuals with FD.

LIMITATIONS OF THE STUDY

The primary limitations of this study are its single-center design and small sample size. A larger multicenter study would be beneficial to further clarify the true prevalence of FD in APS patients and determine whether routine screening should be implemented as part of standard clinical practice.

CONCLUSIONS

Our study highlights the potential coexistence of APS and FD, suggesting that this relationship may be more common than previously recognized. Given the importance of early diagnosis and intervention, awareness of the underdiagnosed nature of FD among APS patients is crucial. Timely identification and management of FDs can significantly improve long-term outcomes and quality of life for those affected.

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