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Functional Tests and Surveys Used to Assess Nervous System Dysfunction in Patients with Fabry Disease – A Review

Stanisław Jesionek,
Pabianice Medical Center Sp. o.o.,
ul. Jana Pawła II 68, 95-200 Pabianice, Poland
https://orcid.org/0009-0004-6026-702X

Maciej Mossakowski,
Central Clinical Hospital of Medical University of Lodz, ul.
Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0008-0423-2083

Martyna Kaźmierczak,
Central Clinical Hospital of Medical University of Lodz, ul.
Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0007-7798-0069

Marta Jajczak,
University Clinical Hospital No.2 of Medical University of Lodz, ul. Żeromskiego 113, 90-549 Łódź, Poland
https://orcid.org/0009-0009-6000-7769

Jakub Parys,
Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0009-1955-7865

Agnieszka Mikosińska,
Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0003-0891-9089

Patrycja Kałuziak,
Charles Jonscher Medical Center, ul. Milionowa 14, 93-113 Łódź, Poland
https://orcid.org/0009-0008-0976-1523

Aleksandra Witek,
Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland
https://orcid.org/0009-0002-1214-2199

Mateusz Litwin,
University Clinical Hospital No.2 of Medical University of Lodz, ul. Żeromskiego 113, 90-549 Łódź, Poland
https://orcid.org/0009-0006-5131-1863

Justyna Jankowska,
Medical University of Lodz al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland
https://orcid.org/0009-0006-0225-2668

Abstract

Introduction and Purpose:

Fabry disease (FD) is a rare, X-linked lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A, leading to progressive multi-organ damage. Among the various complications, autonomic nervous system dysfunction has been suggested as a significant aspect of the disease's pathophysiology. This review aims to evaluate functional tests and surveys used to assess nervous system dysfunction, focusing on the autonomic nervous system in FD patients.

State of Knowledge:

Fabry disease presents with classical and non-classical phenotypes, with early symptoms in males often involving pain, skin lesions, and gastrointestinal disturbances, progressing to more severe manifestations like heart failure and renal disease. The autonomic nervous system, which regulates various physiological processes, may be impaired in Fabry patients, potentially contributing to the disease's symptoms.

Functional tests such are frequently used to assess autonomic function. Studies on autonomic dysfunction in FD have provided mixed results, challenging the assumption that autonomic neuropathy plays a central role in disease progression.
Methods: A comprehensive search of references related to FDe and the autonomic nervous system was conducted on PubMed using the following search terms: "Fabry disease, autonomic nervous system, blood pressure, cold pressor test, vascular manifestations."
Conclusions:
The findings of this review suggest that while autonomic dysfunction may be present in certain subsets of FD patients. Functional tests revealed limited evidence of widespread autonomic dysfunction. QSART showed reduced sweating responses in pain patients but no differences in non-pain patients. These results challenge the widely accepted notion that autonomic neuropathy is a major contributor to Fabry disease symptoms and emphasize the need for further research into the specific mechanisms underlying the disease's clinical manifestations.

Keywords: Fabry disease, autonomic nervous system, blood pressure, cold pressor test

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations in the gene responsible for encoding the lysosomal enzyme alpha-galactosidase A (GLA gene). These mutations lead to a reduction or complete absence of alpha-galactosidase A (α-Gal A) enzyme activity, resulting in the progressive buildup of globotriaosylceramide (GL3 or Gb3) and its deacylated form, globotriaosylsphingosine (lyso-GL3 or Lyso-Gb3), in plasma, urine, and various cells throughout the body. This accumulation primarily affects vascular endothelial cells, podocytes, cardiomyocytes, smooth muscle cells in arteries, and other cell types in organs such as the kidneys and nervous system (1–5).

Clinical Manifestation and Epidemiology

FD presents with clinical variability and progresses slowly. It can be categorized into two phenotypes: the classical form, most commonly seen in men with no residual enzyme activity, and the non-classical (or late-onset) form. Classical FD typically presents in childhood or adolescence with distinctive symptoms such as neuropathic pain, corneal verticillata, and angiokeratoma, as well as gastrointestinal and peripheral nervous system issues like sweating abnormalities. In adults, both classical and late-onset FD can lead to progressive kidney failure, hypertrophic cardiomyopathy, heart rhythm disturbances, and stroke. Men with non-classical FD usually retain some enzyme activity and have lower levels of lyso-Gb3. This form of FD has a more variable disease progression, often affecting only one organ. In females, the disease course can vary widely due to lyonization, ranging from asymptomatic or mild later-onset forms to more severe classical symptoms similar to those seen in male patients.
Prevalence estimates for Fabry disease range from 1 in 8,454 to 1 in 117,000 in males, and it affects various ethnic groups without clear preference. However, recent newborn screening studies suggest higher incidences, ranging from 1 in 3,100 in Italy to 1 in 1,550 in Taiwan, highlighting the potential underdiagnosis of the disease (5–15).
Following review aims to evaluate functional tests used to assess nervous system dysfunction, focusing on the autonomic nervous system in Fabry disease patients.

1) Laser Doppler Velocimetry

Laser Doppler velocimetry is a non-invasive method used to evaluate skin microvasculature and the vasomotor function of sympathetically innervated superficial skin vessels. Sympathetically mediated vasoconstriction is triggered by functional tests (such as the deep breathing test and cold pressor test). Measurements were performed on the great toe and index finger. Cutaneous vasoconstriction is indicated by a reduction in perfusion units relative to baseline perfusion (16).

- **Deep Breathing Test**

  The forced breathing test was performed while the patient was lying down. After 5 minutes of rest, the patient was instructed to perform six consecutive maximal inspiration and expiration cycles at a rate of 6 breaths per minute. The test score was quantified by determining the difference between the maximum and minimum heart rate for each cycle, and the average difference was calculated to obtain the Inspiratory-Expiratory (I-E) difference in beats per minute (17,18).

- **Cold Pressor Test (CPT)**

  The cold pressor test involves immersing a hand or forearm in cold water, a stimulus that causes mild to moderate pain, which is terminated by voluntary withdrawal of the limb. The CPT has been used in studies of pain, autonomic reactivity, and hormonal stress responses (19–21).

Results of Laser Doppler Velocimetry with Deep Breathing and Cold Pressor Tests

The mean baseline superficial skin blood flow in the great toe and index finger was not significantly different between patients and controls. The relative change in blood flow after the cold pressor test did not differ between the two groups, but the deep breathing test caused a significantly larger reduction in blood flow in patients compared to controls. The 19-patient group consisted of 12 patients with painful neuropathy and 7 without. There was a significant reduction in blood flow in pain patients compared to the control group, but no significant difference between non-pain patients and controls. The pain score did not correlate with the decrease in blood flow, suggesting that pain scores should not be used to assess the level of vascular dysfunction (22).

2) Capsaicin Test

The capsaicin test is used to evaluate axonal reflex responses and resulting flare responses by activating the sympathetic nervous system through the application of capsaicin (5% dissolved in ethanol) on the skin. Capsaicin was applied 10 cm above the upper medial edge of the knee and 5 cm above the medial malleolus. Peripheral skin blood flow was measured using laser Doppler. The flare response to capsaicin was calculated as the change from baseline (22).

Results of Capsaicin Test

Baseline blood flow before capsaicin application was lower in patients than in controls. All stimulations caused a significant reduction in blood flow from baseline in both groups. However, the increase in blood flow was significantly smaller in patients, though the spread of blood flow was not significantly different from that of controls. The reduced capsaicin flare response may be linked to dysfunction in the autonomic innervation of skin vessels (22).

3) Ambulatory Blood Pressure, Heart Rate, and Echocardiography Monitoring

Ambulatory monitoring of blood pressure, heart rate, and echocardiography provides valuable information, including determining dipping, non-dipping, or reverse dipping statuses, and measures variability such as standard deviation (SD), coefficient of variation (CV), and average real variability (23).

These parameters were also assessed during functional tests like the standing-up test and forced breathing test.

- **Standing-Up Test**

  After standing up, heart rate increases. The highest heart rate within the first 15 seconds of standing was recorded, and the increase from baseline was calculated. The relative bradycardia was quantified by comparing the highest and lowest heart rates within the first 30 seconds. Heart rate and finger blood pressure were measured 3 minutes after standing. A persistent fall of more than 20 mmHg in systolic pressure or more than 10 mmHg in diastolic pressure after 3 minutes was considered abnormal (24–26).

Results of Blood Pressure, Heart Rate, and Echocardiography Monitoring

The studies suggest that hypertension is rare in Fabry disease patients (27)(28).

One study found that blood pressure measurements were significantly lower in the Fabry disease group compared to controls, except for nighttime systolic blood pressure. There were no significant differences in dipping and non-dipping statuses between Fabry patients and controls. Blood pressure variability measures were similar in both groups, and heart rate variability data showed significantly lower nighttime SD and CV in Fabry patients (23).

Functional tests did not reveal significant abnormalities, suggesting normal autonomic control of the cardiovascular system in Fabry patients. This challenges the widely accepted notion that autonomic neuropathy is a major factor in the pathophysiology of the disease (24).

Quantitative Sudomotor Axon Reflex Test (QSART) – Assessment of Sweating Function

QSART involves inducing sweating through transcutaneous iontophoresis of 5% acetylcholine and is used to evaluate peripheral sudomotor fibers. The test was performed 10 cm above the upper medial edge of the knee and 5 cm above the medial malleolus (22).

Results of QSART

A study showed no difference in baseline sweat volume or latency to sweating onset. However, the total sweat response during 5 minutes of iontophoresis was significantly smaller in patients compared to controls. The total sweat output was significantly lower in the pain group compared to controls, but no difference was observed in the non-pain group. Sweat output also decreased with increasing age in patients but not in controls.

Patients with neuropathic pain had significantly lower sweat responses compared to controls, while no significant difference was observed between controls and patients without neuropathic pain (22).

Autonomic Symptom Profile (ASP)

The Autonomic Symptom Profile (ASP) is used to assess the presence and severity of autonomic symptoms (29). This 73-item questionnaire covers various aspects of autonomic dysfunction, including orthostatic intolerance, vasomotor impairment, secretomotor disorders, gastroparesis, gastrointestinal issues, bladder disorders, and sleep disturbances. The total score is the sum of 11 individual subscales, with a maximum score of 200 for males and 170 for females. A higher score indicates more severe symptoms.

Results of ASP

Gastrointestinal complaints (mainly abdominal pain and diarrhea) were frequently reported in Fabry disease. However, orthostatic intolerance and male sexual dysfunction were less common. Unexpectedly, few Fabry patients reported symptoms in the secretomotor, gastroparesis, diarrhea, and constipation domains. These findings challenge the widely accepted assumption that autonomic neuropathy plays a major role in the pathophysiology of the disease (24).

Conclusions

Patients with Fabry disease form a very heterogeneous group in terms of symptoms and disease progression. Therefore, the results of the studies presented in the studies are ambiguous. Symptoms, and consequently the results of functional tests, may depend on whether patients have been treated with Enzyme Replacement Therapy (ERT) (30–33). However, even in these cases, the effectiveness of therapy does not always correlate with the results of functional tests (24). Some authors also question whether the observed symptoms are the result of autonomic nervous system involvement or whether they are more closely related to damage to the target organs (23,24). This discrepancy underscores the complexity of understanding the disease and highlights the need for further research to clarify the relationship between autonomic dysfunction and the clinical manifestations of Fabry disease.

The heterogeneity of symptoms in Fabry patients also complicates the use of functional tests to monitor disease progression and treatment response. Autonomic tests, such as blood pressure monitoring, heart rate variability, and sweat response assessments, have provided mixed results in Fabry disease, suggesting that the disease affects the autonomic nervous system in a variable manner. These tests may not always be reliable indicators of the severity of autonomic dysfunction or its relationship to other disease manifestations.

Further studies are needed to fully understand the pathophysiology of symptoms related to the autonomic nervous system.

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Authors' contribution:
Conceptualization: Stanisław Jesionek
Methodology: Martyna Kaźmierczak, Stanisław Jesionek
Formal Analysis: Aleksandra Witek, Agnieszka Mikosińska
Sources: Justyna Jankowska, Mateusz Litwin
Visualization: Patrycja Kałuziak, Maciej Mossakowski
Investigation: Jakub Parys, Justyna Jankowska
Supervision: Aleksandra Witek, Martyna Kaźmierczak
Validation: Maciej Mossakowski, Marta Jajczak
Writing – Original Draft: Stanisław Jesionek
Writing – Review & Editing: Agnieszka Mikosińska, Mateusz Litwin
Project administration: Marta Jajczak, Jakub Parys

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