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CASE REPORT

Revisiting the Diagnosis: A Case of Fabry Disease Mimicking Multiple Sclerosis

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Abstract

Fabry disease (FD) is a rare, X-linked lysosomal storage disorder that may mimic multiple sclerosis (MS) due to overlapping neurological symptoms and similar magnetic resonance imaging findings. We report a young man who was initially diagnosed with MS based on sensory symptoms and the presence of white matter lesions. However, the atypical lesion pattern, together with systemic signs including hearing loss and proteinuria, prompted a reevaluation of the diagnosis. Genetic testing confirmed FD, and subsequent family screening identified ten affected relatives, including the patient's mother. This case highlights the importance to recognizing red flags in atypical MS to ensure an accurate diagnosis and the early initaiation of disease-specific treatment.

Keywords: Multiple sclerosis, differential diagnosis, magnetic resonance imaging, Fabry disease

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. Its clinical features and demyelinating lesions frequently overlap with the radiological and clinical presentations of several other diseases, thereby considerably broadening the differential diagnosis (1).

Metabolic disorders, such as Fabry disease (FD), are rare and often overlooked in the differential diagnosis of MS (2). FD is an X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, which result in alpha-galactosidase A deficiency.

This enzymatic deficiency leads to the systemic accumulation of globotriaosylceramide (Gb3) and its derivatives, causing progressive multiorgan dysfunction (3). Endothelial vascular involvement represents the primary pathology, with common manifestations affecting the nervous system, kidneys, heart, eyes, and skin (e.g., cerebrovascular diseases, angiokeratomas, cornea verticillata, proteinuria, and left ventricular hypertrophy). Males are typically more severely affected, whereas heterozygous females may also be symptomatic due to random X inactivation. It is the most common lysosomal storage disorder and has an estimated incidence of 1 in 40,000 (4). Its prevalence is reported as 0.31% in Turkiye among patients receiving renal replacement therapy (5).

White matter lesions resulting from cerebrovascular involvement may mimic demyelinating lesions and consequently lead to misdiagnosis (2). In this case report, we highlight the risk of FD being misdignosed as MS and emphasize the importance of thorough history and rigorous clinical, radiologic, and genetic evaluation to establish the correct diagnosis.

Case Report

A 32-year-old right-handed man presented for a second opinion regarding his diagnosis of MS. His neurological symptoms began at the age of 13 with recurrent, painful, self-limited paresthesias.

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At the age of 20, following the new onset hypoesthesia in the right upper and lower limbs accompanied by diplopia, brain magnetic resonance imaging (MRI) was performed. The MRI revealed T2 hyperintense cortical/juxtacortical and periventricular lesions suggestive of demyelination. Intravenous (IV) corticosteroids were administered with a diagnosis of MS. Cerebrospinal fluid (CSF) examination revealed no oligoclonal bands (OCBs).

Over subsequent years, he experienced similar relapses. Each relapse was treated with IV steroids, resulting in complete recovery, and no disease-modifying therapy was initiated. At the age of 23, when he was admitted to our hospital, neurological examination revealed brisk deep tendon reflexes in the right upper and lower extremities with preserved strength and coordination. Babinski's sign was absent. Distal lower limb paresthesias were present. His past medical history included bilateral hearing loss, and the family history revealed ischemic stroke in his mother.

Spinal MRI revealed no lesions, whereas brain MRI demonstrated stable cortical/juxtacortical and periventricular T2 hyperintense lesions (Figure 1 A-C), with accompanying T1 hypointensity in one lesion and no gadolinium enhancement (Figure 1D). Nerve conduction studies were normal, with no evidence of large fiber neuropathy. Transthoracic echocardiography was unremarkable. Urinalysis revealed proteinuria, which was confirmed by a 24-hour urine protein excretion of 894.6 mg/day. There were no evidence of angiokeratoma, cornea verticillata, or gastrointestinal/autonomic involvement.

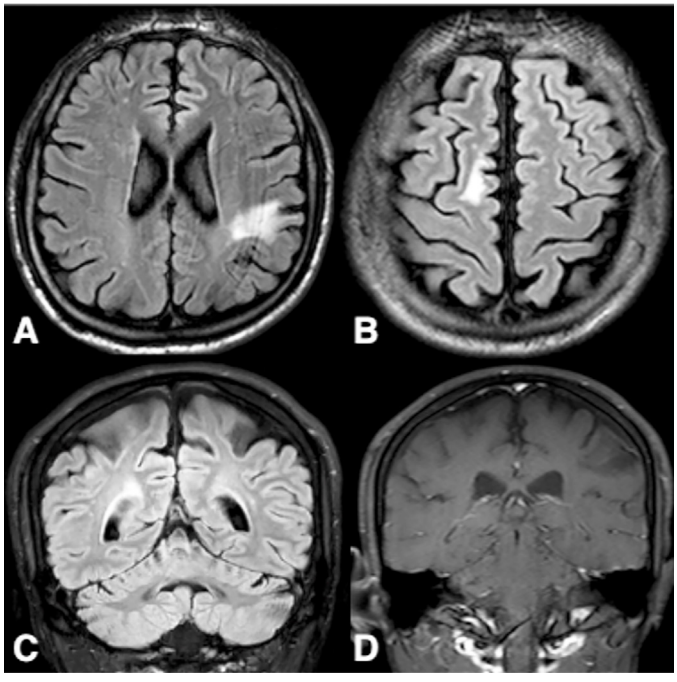

Figure 1. Brain MRI (A,B). Axial T2-FLAIR demonstrate hyperintense lesions in the left frontoparietal cortical/juxtacortical region (A) and the right posterior frontal cortical/juxtacortical region (B). (C) Coronal T2-FLAIR image demonstrates a right periventricular hyperintensity. (D) Coronal postcontrast T1-weighted image demonstrates T1 hypointensity without gadolinium enhancement in the left frontoparietal lesion

MRI: Magnetic resonance imaging, FLAIR: Fluid Attenuated Inversion Recovery

Genetic analysis identified a hemizygous c.680G>A (p.R227Q; p.Arg227Gln) pathogenic variant in the *GLA* gene. Plasma lyso-globotriaosylsphingosine (lyso-Gb3) level were also elevated at 6.4 ng/mL. Together with the systemic findings, these results supported the diagnosis of FD. Subsequent family screening identified FD in ten relatives, including the patient's mother, who carried the same pathogenic variant.

Enzyme replacement therapy (ERT) with agalsidase beta was initiated, and clopidogrel was started for secondary prevention of cerebrovascular events. During follow-up, the patient has remained clinically stable, with preserved cardiac and renal function, absence of recurrent cerebrovascular events, and a marked reduction in painful paresthesias while receiving ERT.

Written informed consent was obtained from the patient.

Discussion

FD frequently presents with neurological involvement, including painful distal paresthesias, small fiber neuropathy, early-onset ischemic stroke, and autonomic dysfunction (3). Typical brain MRI findings in FD include T2 hyperintense lesions located in the subcortical and deep white matter, consistent with an underlying small-vessel vasculopathy. Cerebral microbleeds are commonly observed, whereas haemorrhagic stroke remains rare (6). Additional reported imaging markers include vertebrobasilar dolichoectasia. The pulvinar sign was once considered pathognomonic; however, due to its low incidence and limited diagnostic specificity, it should no longer be regarded as a diagnostic marker (7,8).

From a radiological perspective, FD can closely mimic MS; however, several distinguishing features may assist in differentiation (Table 1). MS typically demonstrates optic nerve, periventricular, juxtacortical, and infratentorial lesions, frequently associated with gadolinium enhancement and common spinal cord involvement. In contrast, Fabry-related lesions are generally diffuse and patchy, exhibit a non-specific distribution, are typically non-enhancing, and usually spare the spinal cord (7,9). More recent studies have further shown that the absence of corpus callosum and infratentorial lesions may aid in differentiating FD from MS (8-10). Furthermore, the central vein sign (CVS), which is characteristic of MS lesions, is absent in FD; in one study, CVS was identified in 78.1% of relapsing-remitting MS lesions (57/73), whereas it was absent in Fabry lesions (0/36) (11). Beyond neuroimaging, CSF-specific OCBs are typically absent in FD. However, as spinal cord imaging and lumbar puncture are not routinely performed during the

Table 1. MRI characteristics to differentiate Fabry disease and multiple sclerosis

Feature	MS	Fabry disease
Lesion distribution	Optic nerve, periventricular, juxtacortical/cortical, infratentorial	Diffuse/patchy, non-specific distribution, supratentorial
Enhancement pattern	Frequent gadolinium enhancement in active lesions	Usually non-enhancing
Corpus callosum involvement	Common	Generally spared
Spinal cord involvement	Common	Generally spared
Central vein sign	Characteristic; present in many lesions	Absent

MS: Multiple sclerosis

diagnostic work up in many centers, the available comparative data remain limited.

Several case reports further illustrate this important diagnostic overlap. In a large Italian family, Russo et al. (12) described the presence of FD and MS in different members, emphasizing the critical role of meticulous neuroimaging review and detailed family history in establishing the correct diagnosis. Saip et al. (13) reported a woman initially misdiagnosed as MS who later developed typical dermatological findings (angiokeratomas) and proteinuria; leading to a confirmed diagnosis of FD through enzyme assay.

Our patient represented the index case of FD within his family. The combination of recurrent diplopia and sensory symptoms, together with periventricular, juxtacortical, and deep white matter lesions, appeared to satisfy dissemination in space and time according to the McDonald criteria, thereby leading to an initial misdiagnosis of MS. However, a definitive diagnosis should only be established after the careful exclusion of alternative causes. In this case, several red flags were already present, including the absence of corpus callosum and spinal cord involvement, a patchy lesion distribution, and the lack of gadolinium enhancement. Furthermore, childhood-onset painful paresthesias—consistent with small fiber neuropathy—together with the absence of CSF-specific OCBs and the presence of systemic features such as bilateral hearing loss and significant proteinuria, collectively argued strongly against a diagnosis of MS. Subsequent genetic analysis confirmed a the presence of pathogenic *GLA* variant.

Although misdiagnosis as MS has been reported more frequently in heterozygous women, adolescent-onset classical FD in a male patient who received multiple high-dose corticosteroid treatments is far less commonly described. This case further demonstrates that, once an index diagnosis is established, cascade family screening can identify multiple previously unrecognized affected relatives, thereby enabling earlier diagnosis and timely initiation of disease-specific therapy, with important public health implications.

This report has several limitations. Small fiber neuropathy was not specifically evaluated, as neither a skin biopsy for the assessment of intraepidermal nerve fiber density nor quantitative sensory testing was performed. This limitation restricts our ability to accurately quantify neuropathic involvement, which is common and frequently an early manifestation of FD, and which cannot be reliably detected by nerve conduction studies alone. Future evaluations incorporating skin biopsy, quantitative sensory testing, or corneal confocal microscopy would allow more precise characterization of small fiber dysfunction and its response to ERT.

Renal involvement was inferred on the basis of proteinuria, and a renal biopsy was not undertaken. In the absence of histopathological confirmation, we were unable to stage renal involvement or document characteristic Gb3/lyso-Gb3 deposition. Although renal biopsy is not always indicated in the presence of a pathogenic *GLA* variant, elevated lyso-Gb3, and stable kidney function, longitudinal monitoring of estimated glomerular filtration rate and proteinuria—and consideration of biopsy in the event of disease progression—would enhance disease staging and prognostic evaluation.

The OCB status was derived solely from patient-reported historical testing and was reported negative; however, the original lumbar puncture report and band count were unavailable, and repeat CSF analysis was not performed.

Conclusion

In conclusion, FD may satisfy the McDonald criteria at an early stage if alternative diagnoses are not actively considered and excluded. Prompt recognition is crucial, as early initiation of disease-specific treatment may improve long-term outcomes and prevent irreversible organ damage. Clinicians should therefore maintain a high index of suspicion for FD in patients presenting with atypical demyelinating features, particularly when systemic findings such as proteinuria or hearing loss are present. The implementation of a simple, low-cost diagnostic pathway may minimize diagnostic delay, facilitate appropriate therapy, and enable timely family counseling.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.C., F.A., A.D., S.D.B., N.E., H.E., Concept: B.C., S.D.B., H.E., Design: B.C., F.A., A.D., S.D.B., H.E., Data Collection or Processing: B.C., F.A., A.D., S.D.B., N.E., Analysis or Interpretation: B.C., S.D.B., N.E., H.E., Literature Search: B.C., F.A., A.D., S.D.B., Writing: B.C., F.A., A.D., S.D.B.

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References

1. Ömerhoca S, Akkaş SY, İçen NK. Multiple sclerosis: diagnosis and differential diagnosis. Noro Psikiyatr Ars. 2018;55:S1-S9.
2. Böttcher T, Rolfs A, Tanislav C, Bitsch A, Köhler W, Gaedeke J, Giese AK, Kolodny EH, Duning T. Fabry disease - underestimated in the differential diagnosis of multiple sclerosis? PLoS One. 2013;28:8:e71894.
3. Ezgü F, Alpsoy E, Bicik Z, Kasapcopur O. Expert opinion on the recognition, diagnosis and management of children and adults with Fabry disease: a multidisciplinary Turkey perspective. Orphanet Journal of Rare Diseases. 2022;17.
4. Berger JR. Misdiagnosis of multiple sclerosis in a female heterozygote with Fabry's disease. Mult Scler Relat Disord. 2019;30:45-47.
5. Yalın SF, Eren N, Sinangil A, Yılmaz VT, Tatar E, Uçar AR, Sevinc M, Can Ö, Gurkan A, Arık N, Ecder SA, Uyar M, Yaşar M, Gülçiçek S, Meşe M, Dheir H, Çakır U, Köksal Cevher Ş, Türkmen K, Güven B, Güven Taymez D, Erkalma Senates B, Ecder T, Koçak H, Uslu A, Demir E, Basturk T, Öğütmen MB, Kınalp C, Dursun B, Biçik Bahçebaşı Z, Sipahi S, Dede F, Oruç M, Çalışkan Y, Genç A, Yelken B, Altıparmak MR, Türkmen A, Seyahi N. Fabry disease prevalence in renal replacement therapy in Turkey. Nephron. 2019;142: 26-33.
6. Kono Y, Wakabayashi T, Kobayashi M, Ohashi T, Eto Y, Ida H, Iguchi Y. Characteristics of cerebral microbleeds in patients with Fabry disease. J Stroke Cerebrovasc Dis. 2016;25:1320-1325.
7. Cocozza S, Russo C, Pontillo G, Pisani A, Brunetti A. Neuroimaging in Fabry disease: current knowledge and future directions. Insights Imaging. 2018;9:1077-1088.
8. Rath J, Foesleitner O, Haider L, Bickel H, Leutmezer F, Polanec S, Arnoldner MA, Sunder-Plassmann G, Prayer D, Berger T, Rommer P, Kasprian G. Neuroradiological differentiation of white matter lesions in patients with multiple sclerosis and Fabry disease. Orphanet J Rare Dis. 2022;17:37.
9. Cocozza S, Olivo G, Riccio E, Russo C, Pontillo G, Ugga L, Migliaccio S, de Rosa D, Feriozzi S, Veroux M, Battaglia Y, Concolino D, Pieruzzi F, Tuttolomondo A, Caronia A, Russo CV, Lanzillo R, Brescia Morra V, Imbriaco M, Brunetti A, Tedeschi E, Pisani A. Corpus callosum involvement: a useful clue for differentiating Fabry disease from multiple sclerosis. Neuroradiology. 2017;59:563-570.
10. Ugga L, Cocozza S, Pontillo G, Russo C, Brescia Morra V, Lanzillo R, Riccio E, Pisani A, Brunetti A. Absence of infratentorial lesions in Fabry disease contributes to differential diagnosis with multiple sclerosis. Brain Behav. 2018;8:e01121.
11. Tranfa M, Tortora M, Pontillo G, Iuzzolino V, Riccio E, Caccavallo S, Di Risi T, Monti S, Lanzillo R, Brescia Morra V, Palma G, Petracca M, Pisani A, Brunetti A, Cocozza S. The central vein sign helps in differentiating multiple sclerosis from its mimickers: lessons from Fabry disease. Eur Radiol. 2022;32:3846-3854.
12. Russo C, Riccio E, Pontillo G, Cocozza S, Tedeschi E, Centonze D, Pisani A. Multiple sclerosis and Fabry disease, two sides of the coin? The case of an Italian family. Mult Scler Relat Disord. 2018;26:164-167.
13. Saip S, Uluduz D, Erkol G. Fabry disease mimicking multiple sclerosis. Clin Neurol Neurosurg. 2007;109:361-363.