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DIAGNOSTIC NEURORADIOLOGY

Corpus callosum involvement: a useful clue for differentiating Fabry Disease from Multiple Sclerosis

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Abstract

Purpose Multiple sclerosis (MS) has been proposed as a possible differential diagnosis for Fabry disease (FD). The aim of this work was to evaluate the involvement of corpus callosum (CC) on MR images and its possible role as a radiological sign to differentiate between FD and MS.

Methods In this multicentric study, we retrospectively evaluated the presence of white matter lesions (WMLs) on the FLAIR images of 104 patients with FD and 117 patients with MS. The incidence of CC-WML was assessed in the two groups and also in a subgroup of 37 FD patients showing neurological symptoms.

Results WMLs were detected in 50 of 104 FD patients (48.1%) and in all MS patients. However, a lesion in the CC was detected in only 3 FD patients (2.9%) and in 106 MS patients (90.6%). In the FD subgroup with neurological symptoms, WMLs were present in 26 of 37 patients (70.3%), with two subjects (5.4%) showing a definite callosal lesion.

Conclusion FD patients have a very low incidence of CC involvement on conventional MR images compared to MS, independently from the clinical presentation and the overall degree of WM involvement. Evaluating the presence of CC lesions on brain MR scans can be used as a radiological sign for a differential diagnosis between MS and FD, rapidly addressing the physician toward a correct diagnosis and subsequent treatment options.

Keywords MRI · Corpus callosum · Fabry disease · Multiple sclerosis

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Abbreviations

MS	Multiple sclerosis
FD	Fabry disease
CC	Corpus callosum;
WMLs	White matter lesions
eGFR	Estimated glomerular filtration rate
CKD-	Chronic Kidney Disease Epidemiology
EPI	Collaboration
GLA	α-Galactosidase A
ERT	Enzyme replacement therapy
DD	Disease duration
EDSS	Expanded Disability Status Scale
ARR	Annualized Relapse Rate
MSSS	Multiple Sclerosis Severity Score
CSF	Cerebrospinal fluid

Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by mutation in the α-galactosidase A (GLA) gene, resulting in a lack, or deficiency, of the enzyme GLA, with consequent progressive accumulation of the undegraded glycosphingolipids in different tissues [1]. Clinical presentation of FD includes autonomic neuropathies, along with a systemic involvement, affecting kidney, hearth, gastrointestinal system, and brain [2].

Cerebral involvement in FD is mainly caused by cerebrovascular complications, based on the cerebral vasculopathy known to be present in the disease [3], mainly due to both the progressive glycosphingolipid accumulation in vessels and to the secondary arrhythmic cardiac involvement. These include stroke, which is the most prevalent cerebrovascular event in FD [4], along with the presence of white matter lesions (WMLs), often clinically asymptomatic in these patients [5].

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease of the central nervous system (CNS) characterized by demyelination and axonal loss [6]. On MR scan, MS is characterized by the presence of demyelinating plaques in characteristic locations, such as juxtacortical, periventricular, infratentorial, and spinal cord [7]. In particular, corpus callosum (CC) involvement is typical in MS, since up to the 95% of MS patients show abnormalities of this region on conventional MRI sequences [8–10]. However, CC involvement is not pathognomonic or exclusive of MS, due to its presence in other demyelinating and inflammatory diseases of the CNS [11].

Even if different patterns of systemic and neurological manifestations are present in these two conditions, due to the incidence of WMLs in FD, MS has been proposed as a possible differential diagnosis [12, 13]. Misdiagnosis of MS could lead to a delayed start or even a wrong treatment option;

therefore, the search for a sign, which can allow a differential diagnosis between these two conditions, is crucial.

To date, an evaluation of incidence of WMLs of the CC of FD patients has never been performed. The aim of this work was to evaluate the involvement of CC on conventional MR images and its possible role as a radiological sign for a differential diagnosis between FD and MS. With this aim, we retrospectively evaluated 104 and 117 brain MR scans of FD and MS patients, respectively, to determine the incidence of WMLs in the CC of these patients.

Methods

Subjects

In this multicentric retrospective study, we analyzed a cohort of FD patients recruited through the FD specialized care clinics of seven hospitals. The clinical and radiological data collected in this study were obtained at different centers as part of the clinical workup deemed necessary for each patient, and only the authorization for transferral of data was obtained from the Local Ethical Committee of the coordinating center.

Inclusion criteria were as follows: genetically proven FD, availability of brain MRI scans, and signed informed consent for participation in the study. Diagnosis of FD was confirmed using biochemical or genetic testing, and both adult male and female participants were approached to participate, without age limitations. Indications for brain MRI varied between and within centers including but not limited to routine screening scans, headache, transient neurologic symptoms, and acute stroke evaluations.

Age was recorded at the time of the brain MR scan. Hypertension, diabetes mellitus, cardiac arrhythmia, left ventricular hypertrophy, renal failure (considered as present when the estimated glomerular filtration rate—eGFR—of the patient was <90 ml/min), proteinuria (considered as present when the patient scored a value >150 mg/24 h), and the presence of neurological symptoms (including stroke, cephalalgia, acroparesthesia, etc.) were recorded based on the prior diagnosis at each specialized care center participating in this study. History of FD-associated pain in hands and feet, decreased sweating, and gastrointestinal problems characteristic for FD were also recorded for each participant. Finally, history of prior stroke or transient ischemic attacks, hemodialysis, renal or cardiac transplant, current use of tobacco or alcohol, and treatment with enzyme replacement therapy (ERT) were abstracted by a clinician experienced in FD from medical records or obtained in direct interviews.

Renal function was expressed as eGFR, calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14]. Other laboratory values were measured using standard hospital laboratory techniques. GLA enzyme

activity was classified as "absent" (<1% of normal values) or "residual" (1–5% of normal values), because of the different measurement methods used in the recruiting centers (plasma, leukocytes, etc.).

Data were recorded by each center in dedicated case report forms and then entered into a central database at the coordinating center, according to good clinical practice guidelines.

From the whole FD group, a subgroup of patients with neurological symptoms was identified in order to determine the incidence of CC lesions in a group of subjects in which a suspect of MS could have been clinically hypothesized.

Along with FD patients, the MR brain scans of a group of relapsing remitting-MS patients, acquired in a single center on different scanner, were selected of comparable age and sex with the group of FD patients, and analyzed in this study. All MS patients fulfilled the revised McDonald criteria for MS diagnosis [15]. Clinical variables were retrospectively collected from clinical records within 2 weeks from the MR scan. These included, along with disease duration (DD), measures from the first occurrence of symptoms clearly related to the disease: Expanded Disability Status Scale (EDSS), Annualized Relapse Rate (ARR), and Multiple Sclerosis Severity Score (MSSS).

MRI data evaluation

For all subjects included in the analysis, MRI brain scans were visually assessed by two neuroradiologists, blinded for the diagnosis and in consensus (A.B. and E.T.), who rated the presence and the load of WMLs as suggested by a recent multicenter MR study on FD [16]. Briefly, this score identifies the presence of WMLs, depending on the anatomical localization, in periventricular and deep hemispheric white matter. For each locations, a score ranging from 0 to 3 (with 0 indicating absence of WMLs, and 3 largest and confluent chronic WMLs) was given, with a single subject who could therefore in our study range from a minimum of 0 (indicating absence of WMLs) to 6.

The evaluation of possible WMLs was carried out on fluid-attenuated inversion recovery (FLAIR) images acquired, depending on the scanner, with different orientations on ≤5 mm-thick slices at ≥0.5 Tesla. A complete list of all the subjects included in this study grouped according to MR scanner field strength is reported in Table 1.

The visual assessment of CC involvement was performed considering all FLAIR images available per patient, evaluating the portion of CC running from the midline to a plane passing through the external wall of the lateral ventricles on both sides. Sagittal planes were visually investigated firstly. Where available, axial and coronal FLAIR images were also inspected, to confirm the data recorded on the sagittal plane. Where 3D-FLAIR images were available, multiplanar

Table 1 Subjects included in this study grouped according to MR scanner field strength

	FD	MS
0.5 Tesla	28/104	na
1.5 Tesla	41/104	32/117
3 Tesla	35/104	85/117

FD Fabry disease, *MS* multiple sclerosis, *na* not applicable

reconstructions were generated and all three planes were inspected, starting from the sagittal one.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Science (SPSS) package (SPSS Inc., version 17.0, Chicago, IL). An unpaired *t* test was used for comparing ages and Fazekas scores between the FD and the MS groups, while a chi-squared test was used to determine differences in term of sex. A $p = 0.05$ was set to indicate a statistically significant difference. Finally, no Cohen's coefficient was needed to evaluate the performance of the evaluation, since the two neuroradiologists performed the analysis in consensus.

Results

One hundred and four FD patients (64 women, 61.5%) were included in the study. Mean age was 43 years (with a standard deviation of 13.4 years), ranging from 13 to 72 years. Activity of the GLA enzyme was absent in 29 patients (27.9%), while it showed a residual activity in 75 patients (72.1%); distinct GLA gene mutations were represented and the clinical manifestations were different, with multiple organ involvement. Finally, 72 patients were treated with ERT (69.2%, with a mean duration of 58.9 ± 69.5 months). Demographic and clinical information of all FD patients included in the analysis are listed in Table 2, while a complete list of the different genetic mutations is reported in Table S1 of the Supplementary Materials.

Along with the FD patients, 117 MS patients (79 women, 67.5%) were included in the study. Mean age was 38 years (with a standard deviation of 11.1 years), ranging from 12 to 65 years. These patients showed a mean DD of 6.3 years, and a mean EDSS score of 3.4. Complete demographic and clinical information of MS patients included in the analysis are listed in Table 3. The FD and MS groups were not significantly different for age and sex.

From the 104 FD patients, a subgroup of 37 subjects with neurological symptoms was identified (M/F = 13/24). Mean age of this subgroup of patients was 46 years (with a standard deviation of 12.6 years), ranging from 17 to 72 years. Activity

Table 2 Subjects demographic and clinical variables of all FD patients included in the study

	FD (all patients)	FD (with neurological symptoms)
Age (mean ± SD)	43 ± 13.4 (range 13–72)	46 ± 12.6 (range 17–72)
Sex (M/F)	40/64	13/24
Neurological symptoms	37/104	na
Hypertension	24/104	16/37
Diabetes	3/104	2/37
Arrhythmia	7/104	3/37
Left ventricular hypertrophy	51/104	21/37
Renal failure	48/104	21/37
Proteinuria	49/104	18/37
Tabagism	9/104	4/37

Age is expressed in years

FD Fabry disease, *SD* standard deviation, *na* not applicable

of the GLA enzyme was absent in 12 patients (32.4%), and residual in the remaining 25 patients (67.6%). Similarly to the entire group, distinct GLA gene mutations were represented and the clinical manifestations were different, with multiple organ involvement. Finally, a total of 30 patients (81.1%) were under treatment with ERT (with a mean duration of 64.3 ± 59.1 months). Demographic and clinical information of the FD patents with neurological symptoms included in the analysis are also listed in Table 2.

Among the total of 104 FD patients, WMLs were detected in 50 subjects (48.1%), with a mean Fazekas score of 2.3 (±1.71). In the entire FD population, a lesion in the CC was detected in only three subjects (2.9%) (Table 4). An example of WML load in FD patients is shown in Fig. 1.

All MS patients showed some WMLs in the periventricular or deep WM regions, with a mean Fazekas score of 2.6 (±1.27), not significantly different from that of FD patients. Instead, the incidence of lesions in the CC was significantly higher in the MS group compared to FD, with at least one definite callosal lesion present in 106 of 117 MS patients (90.6%) (Table 4).

In the subgroup of 37 FD patients with neurological symptoms, WMLs were present in 26 subjects (70.3%), with a mean Fazekas score (2.5 ± 1.94) similar to the one of the other two groups. Even in neurologically symptomatic FD patients, a low incidence of CC lesion was observed, with only two subjects (5.4%) showing a definite WML at that level.

The individual Fazekas scores of the three patients with a CC lesion were 1, 3, and 5, respectively, with a mean value of 3.0.

Measures of diagnostic performance relative to CC involvement in the clinical setting of a differential diagnosis between MS and FD are listed in Table 5.

Finally, when analyzing the MR characteristic of the callosal lesions in FD, no WML affecting the CC resembled the typical appearance of a demyelinating plaque, in terms neither of anatomical location nor of morphological appearance (Fig. 2).

Discussion

This is, to the best of our knowledge, the first study that investigates the incidence of WMLs in the CC in a relatively large group of FD patients with the aim of looking for a radiological sign that may help to distinguish this disease from MS. We have shown that in FD patients, CC is very rarely involved on conventional MR images compared to MS,

Table 3 Subjects demographic and clinical variables of MS patients included in the study

	MS
Age (mean ± SD)	38 ± 11.1 (range 12–65)
Sex (M/F)	38/79
DD (mean ± SD)	6.3 ± 7.3
EDSS (median)	3.25 (range 1.5–7.0)
ARR (median)	0.60 (range 0.17–4.03)
MSSS (median)	4.68 (range 1.15–8.70)

Age and DD are expressed in years

MS multiple sclerosis, *SD* standard deviation, *EDSS* Expanded Disability Status Scale, *ARR* Annualized Relapse Rate, *MSSS* Multiple Sclerosis Severity Score, *DD* disease duration. *SD* standard deviation

Table 4 Distribution of CC involvement in FD and MS patients

	FD	MS	TOT
Positive CC involvement	3	106	109
Negative CC involvement	101	11	112
TOT	104	117	221

CC Corpus callosum, *FD* Fabry disease, *MS* multiple sclerosis

Fig. 1 Axial FLAIR images of two FD patients (**a-b**) with a Fazekas score of 6, showing confluent areas of white matter hyperintensity. In both cases, the corpus callosum is spared from white matter lesions (not shown)
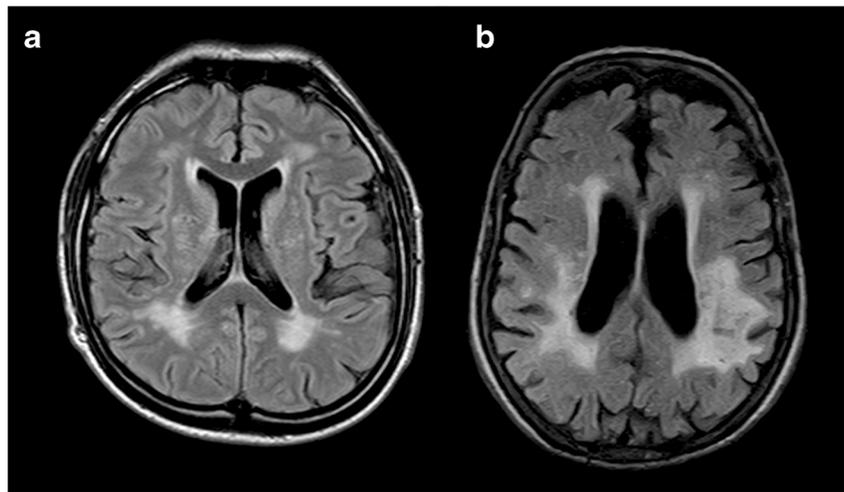
independently from the clinical presentation, and that this evaluation can be used to differentiate MS from FD patients.

Neuropathology studies have shown that glycosphingolipid storage in FD is not restricted to the vascular bed, but it is present in different brain regions which are typically affected by neurodegenerative disorders [17, 18]. Despite the poorly understood physiopathological mechanisms of this phenomenon, the cerebrovascular involvement present in FD induces alterations radiologically identified as WMLs, considered a characteristic FD neuroradiological sign [19]. A recent study showed that age and prior history of stroke were predictors of the WML load in FD, while cardiac involvement and treatment with ERT were associated, respectively, with a higher and a lower WML burden [20].

In the last years, FD has been proposed as a possible differential diagnosis for MS, due to the heterogeneity and the overlap of the clinical presentation of both disorders [12, 13]. Brain MR is usually performed in FD, and in some patients, WM abnormalities are present, showing a pattern somehow similar between MS and FD. Indeed, the load of WMLs may mimic the appearance of MS [3]; thus, a careful differential diagnosis should be performed. However, to date, a definite sign that could help in a radiological differential diagnosis between these two conditions is lacking.

The involvement of CC in MS is a typical feature of the disease [8–10]. MS lesions in CC may show some degrees of heterogeneity, being present as narrow hyperintense band along the undersurface (calloso-septal interface) of CC, or as radiated T2w-hyperintensity going from the undersurface to the deep callosal fibers, or as ovoid lesions which radiates into the pericallosal WM, known as Dawson's fingers [9, 21, 22]. However, it is also well known that CC involvement is not specific of MS, being present in other neuroinflammatory or acquired demyelinating diseases, such as neuromyelitis optica, acute disseminated encephalomyelitis, Susac's syndrome, CNS vasculitis, and systemic lupus erythematosus [11].

To date, no studies have been performed on large number of FD patients to evaluate the incidence of CC involvement in this disease, and its possible role in the differential diagnosis with MS. Indeed, this possibility has been only suggested in a previous work [12], but never formally tested in two groups of FD and MS patients.

Different case reports in the last years reported the initial misdiagnosis of MS in subjects who, later, turned out to be FD patients [23–26]. In these cases, patients did not show CC involvement, with WMLs being variably present in juxtacortical areas, periventricular WM, basal ganglia, pons, and cerebellar WM. Interestingly, in another case report [27], few T2-hyperintense lesions involving the CC were reported in a patient later diagnosed with a coexistence of both MS and FD, allowing us to speculate that the involvement of CC was indeed linked to MS, rather than FD.

On reflection, in a recent case report [28], a patient with FD showed CC involvement on FLAIR images. This finding is only apparently in conflict with ours. In fact, as the involvement of CC in FD is very infrequent (2.9%), but not totally absent, this result may fall in the low rate of false positive cases, in which a complementary examination, such as a spine MRI (which has already been suggested to help in

Table 5 Measures of diagnostic performance for CC involvement in the clinical setting of differential diagnosis between MS and FD

Sensitivity	91%
Specificity	97%
Positive predictive value (PPV)	97%
Negative predictive value (NPV)	90%
Accuracy	94%
Positive likelihood ratio	30.33
Negative likelihood ratio	0.09

Fig. 2 Sagittal (**a**) 3D-FLAIR and the corresponding coronal MPR (**b**) of an FD patient, with a Fazekas score of 3, showing a white matter lesion in the right aspect of the body of the corpus callosum (*arrows*)
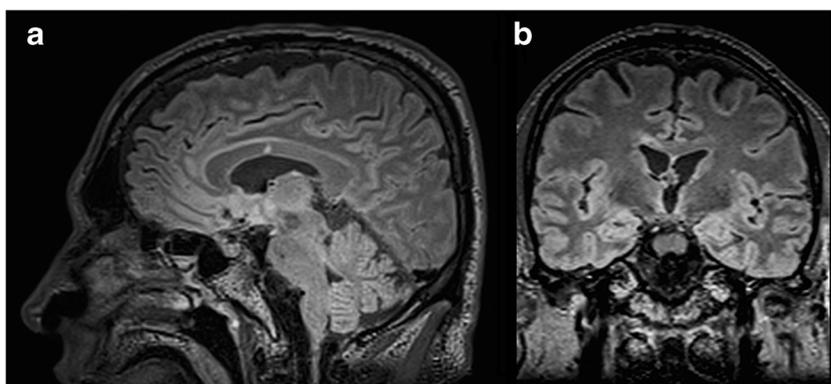
distinguishing between MS and FD [12]), could help to raise the accuracy of MRI in this differential diagnosis.

Furthermore, it should be noted that in the three cases of positive CC involvement in FD patients, these lesions did exhibit neither anatomical localization nor morphological features of a classic MS plaque (e.g., perivenular location, Dawson's fingers). This finding, together with the low WML load of these patients, allows for an even stronger speculation about the high positive predictive value of this sign in excluding MS from the possible differential diagnosis of FD.

Along with the evaluation of WMLs by means of conventional MRI, microstructural WM changes have been detected in FD independent of the presence of WMLs in most, but not all, studies [29–32]. In particular, both a reduction of the fractional anisotropy and an increase in the mean diffusivity in the CC were found in FD patients suggesting that even if clear lesions are not visible on conventional MRI, CC is not completely spared by the disease. Due to the retrospective nature of the present work, however, we were not able to explore the degree of microstructural changes in those patients who showed an involvement on conventional MRI. For this reason, further studies should be performed to investigate a possible relationship between the involvement of CC on conventional MRI and the microstructural changes by means of a diffusion tensor imaging analysis.

In addition, other biochemical and neuroradiological findings have been suggested as useful when considering a possible differential diagnosis between these two conditions. In particular, the presence of oligoclonal bands in the cerebrospinal fluid (CSF) and the evidence of hyperintense spinal lesions on MRI scan have both been reported as uncommon findings in FD [12]. However, both these procedures are not routinely performed in the diagnostic workup of FD patients, and therefore, their utility is relatively limited in daily clinical practice. Our results fill this gap, providing an easy to identify finding that can be used as a radiological sign for differential diagnosis between MS and FD on the routinely performed brain MR scans. Nonetheless, to further elucidate the possible relations between CSF data abnormalities, spinal cord lesions, and CC involvement in these two populations and their combined

diagnostic accuracy, future multimodal longitudinal studies are warranted.

Some further limitations should be considered in the present study. In particular, due to the multicentric nature of our retrospective report, the FLAIR images used for the evaluation were not acquired on the same scanner or with the same geometry, in terms of both spatial resolution and orientation planes. Indeed, not all MR scans included a sagittal FLAIR (or a 3D-FLAIR, which could allow for a multiplanar reconstruction), which is known to reliably detect CC lesions [33, 34]. However, this occurred in only 21 of our 104 subjects (20.2%), while in the majority of the cases, a sagittal FLAIR sequence was available, or a 3D geometry was used, with a voxel size of $1 \times 1 \times 1$ mm^3. To test if the use of 3D-FLAIR could help the neuroradiologists in detecting smaller WMLs in FD, thus increasing the rate of lesion detection in the CC, further prospective studies should be performed.

Another limitation, always referable to the retrospective nature of the study, has to be researched in the different proportion of MR scans performed at various field strengths between the two groups, which could lead to a possible bias given the inferior sensitivity of 0.5 T MRI for WML detection compared to high field scanners. Indeed, an ancillary analysis performed to compare the incidence of CC lesions in the subgroup of patients studied on the same 3T scanner (35 FD vs 85 MS patients) showed a similar results in the detection of callosal lesions in the two groups (data not shown). However, prospective studies with the inclusion of MS acquired on low field scanner are warranted to confirm our results.

Furthermore, the inclusion of MS patients with definite diagnosis, according to the McDonald criteria [35], may have led to a higher incidence of callosal lesion in our control group. However, our sample of MS patients had a similar WML load in both periventricular and deep white matter regions. Although the Fazekas score was not created to quantify the WML load in MS, we used it to compare these two groups, and only 5 out of 117 MS subjects (4.3%) scored a Fazekas of 6, therefore suggesting a heavy WML burden. However, to further clarify the role of the evaluation of CC as a radiological

sign for the differential diagnosis between MS and FD, a prospective study with the inclusion of probable MS patients should be performed. Moreover, even if the Fazekas score has proved to be close correlated to quantitative measurements [36], it only allows for a visual assessment of the lesion load and that more objective and quantifiable methods are available to quantify the WML burden.

However, again due to the retrospective nature of our study, 3D-FLAIR imaging, which is very suitable for this analysis, was available only in 34 of our 104 FD patients (32.7%). For these reasons, future prospective studies with objective and quantifiable assessment of the lesion load may be performed to confirm our results.

Conclusions

In conclusion, we showed that FD patients show a very low incidence of CC involvement on conventional MRI images compared to MS and that the presence of callosal lesions is somehow independent by the clinical presentation. Our result proves that the evaluation of CC can be used as a radiological sign for differential diagnosis between MS and FD, rapidly addressing the physician toward a correct diagnosis and subsequent treatment options.

References

1. Zarate YA, Hopkin RJ (2008) Fabry's disease. Lancet 372(9647): 1427–1435. doi:10.1016/S0140-6736(08)61589-5
2. Ishii S, Chang HH, Kawasaki K, Yasuda K, Wu HL, Garman SC, Fan JQ (2007) Mutant alpha-galactosidase A enzymes identified in Fabry disease patients with residual enzyme activity: biochemical characterization and restoration of normal intracellular processing by 1-deoxygalactonojirimycin. Biochem J 406(2):285–295. doi:10.1042/BJ20070479
3. Kolodny E, Fellgiebel A, Hilz MJ, Sims K, Caruso P, Phan TG, Politei J, Manara R, Burlina A (2015) Cerebrovascular involvement in Fabry disease: current status of knowledge. Stroke 46(1):302–313. doi:10.1161/STROKEAHA.114.006283
4. Sims K, Politei J, Banikazemi M, Lee P (2009) Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. Stroke 40(3):788–794. doi:10.1161/STROKEAHA.108.526293
5. Fellgiebel A, Muller MJ, Ginsberg L (2006) CNS manifestations of Fabry's disease. Lancet Neurol 5(9):791–795. doi:10.1016/S1474-4422(06)70548-8
6. Compston A, Coles A (2008) Multiple sclerosis. Lancet 372(9648): 1502–1517. doi:10.1016/S0140-6736(08)61620-7
7. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, Rovira A, Sastre-Garriga J, Tintore M, Frederiksen JL, Gasperini C, Palace J, Reich DS, Banwell B, Montalban X, Barkhof F (2016) MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 15(3):292–303. doi:10.1016/S1474-4422(15)00393-2
8. Gean-Marton AD, Vezina LG, Marton KI, Stimac GK, Peyster RG, Taveras JM, Davis KR (1991) Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis. Radiology 180(1): 215–221. doi:10.1148/radiology.180.1.2052698
9. Palmer S, Bradley WG, Chen DY, Patel S (1999) Subcallosal striations: early findings of multiple sclerosis on sagittal, thin-section, fast FLAIR MR images. Radiology 210(1):149–153. doi:10.1148/radiology.210.1.r99ja38149
10. Simon JH, Holtas SL, Schiffer RB, Rudick RA, Herndon RM, Kido DK, Utz R (1986) Corpus callosum and subcallosal-periventricular lesions in multiple sclerosis: detection with MR. Radiology 160(2): 363–367. doi:10.1148/radiology.160.2.3726114
11. Garg N, Reddel SW, Miller DH, Chataway J, Riminton DS, Barnett Y, Masters L, Barnett MH, Hardy TA (2015) The corpus callosum in the diagnosis of multiple sclerosis and other CNS demyelinating and inflammatory diseases. J Neurol Neurosurg Psychiatry 86(12): 1374–1382. doi:10.1136/jnnp-2014-309649
12. Bottcher T, Rolfs A, Tanislav C, Bitsch A, Kohler W, Gaedeke J, Giese AK, Kolodny EH, Duning T (2013) Fabry disease—underestimated in the differential diagnosis of multiple sclerosis? PLoS One 8(8):e71894. doi:10.1371/journal.pone.0071894
13. Callegaro D, Kaimen-Maciel DR (2006) Fabry's disease as a differential diagnosis of MS. Int MS J 13(1):27–30
14. Vucic Lovrencic M, Radisic Biljak V, Bozicevic S, Prasek M, Pavkovic P, Knotek M (2012) Estimating glomerular filtration rate (GFR) in diabetes: the performance of MDRD and CKD-EPI equations in patients with various degrees of albuminuria. Clin Biochem 45(18):1694–1696. doi:10.1016/j.clinbiochem.2012.07.115
15. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69(2):292–302. doi:10.1002/ana.22366
16. Fazekas F, Enzinger C, Schmidt R, Grittner U, Giese AK, Hennerici MG, Huber R, Jungehulsing GJ, Kaps M, Kessler C, Martus P, Putaala J, Ropele S, Tanislav C, Tatlisumak T, Thijs V, von Sarnowski B, Norrving B, Rolfs A (2015) Brain magnetic resonance imaging findings fail to suspect Fabry disease in young patients with an acute cerebrovascular event. Stroke 46(6):1548–1553. doi:10.1161/STROKEAHA.114.008548
17. deVeber GA, Schwarting GA, Kolodny EH, Kowall NW (1992) Fabry disease: immunocytochemical characterization of neuronal involvement. Ann Neurol 31(4):409–415. doi:10.1002/ana.410310410
18. Kaye EM, Kolodny EH, Logigian EL, Ullman MD (1988) Nervous system involvement in Fabry's disease: clinicopathological and biochemical correlation. Ann Neurol 23(5):505–509. doi:10.1002/ana.410230513
19. Moore DF, Altarescu G, Barker WC, Patronas NJ, Herscovitch P, Schiffmann R (2003) White matter lesions in Fabry disease occur in 'prior' selectively hypometabolic and hyperperfused brain regions. Brain Res Bull 62(3):231–240

20. Rost NS, Cloonan L, Kanakis AS, Fitzpatrick KM, Azzariti DR, Clarke V, Lourenco CM, Germain DP, Politei JM, Homola GA, Sommer C, Uceyler N, Sims KB (2016) Determinants of white matter hyperintensity burden in patients with Fabry disease. Neurology 86(20):1880–1886. doi:10.1212/WNL.0000000000002673

21. Hashemi RH, Bradley WG Jr, Chen DY, Jordan JE, Queralt JA, Cheng AE, Henrie JN (1995) Suspected multiple sclerosis: MR imaging with a thin-section fast FLAIR pulse sequence. Radiology 196(2):505–510. doi:10.1148/radiology.196.2.7617868

22. Horowitz AL, Kaplan RD, Grewe G, White RT, Salberg LM (1989) The ovoid lesion: a new MR observation in patients with multiple sclerosis. AJNR Am J Neuroradiol 10(2):303–305

23. Becker J, Rolfs A, Karabul N, Berlit P, Kraemer M (2016) D313Y mutation in the differential diagnosis of white matter lesions: experiences from a multiple sclerosis outpatient clinic. Mult Scler. doi:10.1177/1352458516638747

24. Gregoire SM, Brown MM, Collas DM, Jacob P, Lachmann RH, Werring DJ (2009) Posterior circulation strokes without systemic involvement as the presenting feature of Fabry disease. J Neurol Neurosurg Psychiatry 80(12):1414–1416. doi:10.1136/jnnp.2008.158790

25. Lehmann HC, Hengge UR, Alswede L, Saleh A, von Geldern G, Hartung HP, Ruzicka T, Hemmer B (2006) A 32-year-old man with relapsing-progressive brainstem symptoms. Lancet Neurol 5(1):97–102. doi:10.1016/S1474-4422(05)70287-8

26. Saip S, Uluduz D, Erkol G (2007) Fabry disease mimicking multiple sclerosis. Clin Neurol Neurosurg 109(4):361–363. doi:10.1016/j.clineuro.2006.12.006

27. Invernizzi P, Bonometti MA, Turri E, Benedetti MD, Salviati A (2008) A case of Fabry disease with central nervous system (CNS) demyelinating lesions: a double trouble? Mult Scler 14(7):1003–1006. doi:10.1177/1352458508092355

28. Shribman SE, Shah AR, Werring DJ, Cockerell OC (2015) Fabry disease mimicking multiple sclerosis: lessons from two case reports. Mult Scler Relat Disord 4(2):170–175. doi:10.1016/j.msard.2015.01.001

29. Albrecht J, Dellani PR, Muller MJ, Schermuly I, Beck M, Stoeter P, Gerhard A, Fellgiebel A (2007) Voxel based analyses of diffusion tensor imaging in Fabry disease. J Neurol Neurosurg Psychiatry 78(9):964–969. doi:10.1136/jnnp.2006.112987

30. Fellgiebel A, Mazanek M, Whybra C, Beck M, Hartung R, Muller KM, Scheurich A, Dellani PR, Stoeter P, Muller MJ (2006) Pattern of microstructural brain tissue alterations in Fabry disease: a diffusion-tensor imaging study. J Neurol 253(6):780–787. doi:10.1007/s00415-006-0118-y

31. Paavilainen T, Lepomaki V, Saunavaara J, Borra R, Nuutila P, Kantola I, Parkkola R (2013) Diffusion tensor imaging and brain volumetry in Fabry disease patients. Neuroradiology 55(5):551–558. doi:10.1007/s00234-012-1131-8

32. Underhill HR, Golden-Grant K, Garrett LT, Uhrich S, Zielinski BA, Scott CR (2015) Detecting the effects of Fabry disease in the adult human brain with diffusion tensor imaging and fast bound-pool fraction imaging. J Magn Reson Imaging 42(6):1611–1622. doi:10.1002/jmri.24952

33. Simon JH, Li D, Traboulsee A, Coyle PK, Arnold DL, Barkhof F, Frank JA, Grossman R, Paty DW, Radue EW, Wolinsky JS (2006) Standardized MR imaging protocol for multiple sclerosis: consortium of MS centers consensus guidelines. AJNR Am J Neuroradiol 27(2):455–461

34. Traboulsee A, Li DK (2008) Conventional MR imaging. Neuroimaging Clin N Am 18(4):651–673 . doi:10.1016/j.nic.2008.07.001x

35. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 50(1):121–127

36. Hernández V, Morris Z, Dickie DA, Royle NA, Munoz Maniega S, Aribisala BS, Bastin ME, Deary IJ, Wardlaw JM (2012) Close correlation between quantitative and qualitative assessments of white matter lesions. Neuroepidemiology 40(1):13–22