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Vertebrobasilar Dolichoectasia in Fabry Disease: The Earliest Marker of Neurovascular Involvement?

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Abstract

Introduction: Fabry disease (FD) is a lysosomal storage disorder associated with marked cerebrovascular involvement. Conventional magnetic resonance imaging (MRI) shows different abnormalities, like white matter lesions that may already be present at an early stage in the disease. **Aim:** To present observations from a series of brain MRIs performed among a cohort of patients with FD and the relationship of imaging abnormalities with the presence of cardiovascular risk factors (CVRFs). **Methods:** A total of 70 patients with FD (43 women) were enrolled. The cardiac, renal, ophthalmic, and peripheral nerve functioning was assessed. The MRI evaluation included assessment for evidence of ischemia, microbleeds, pulvinar sign, Arnold-Chiari type I malformation, and vertebrobasilar dolichoectasia (VBD). The presence or absence of CVRFs was examined for all patients. **Results:** Renal involvement was found in 60%, cardiac compromise in 30%, cornea verticillata in 91.4%, and acroparesthesias in 87.1% of patients. Brain MRI analysis found evidence of cerebral ischemic injury in 25.9% of men and 30.2% of women. Vertebrobasilar dolichoectasia was observed in imaging from 55.5% of men and 34.8% of women. The logistic regression analysis adjusted for cardiovascular risks factors, using ischemia or VBD as a dependent variable, showed no statistically significant results. **Discussion:** Our results have demonstrated cerebrovascular involvement before the third decade in many patients with FD. This study is further evidence confirming that women are not just carriers of FD and should be followed clinically and evaluated comprehensively to monitor for disease burden and progression. Although silent brain ischemias in MRI should be included as a key feature for the diagnoses of FD, VBD is an earlier and frequent sign.

Keywords

Fabry disease, vertebrobasilar dolichoectasia, stroke, Fabry MRI, brain ischemia

Introduction

Fabry disease (FD) is an X-linked disorder that results from the presence of a pathogenic mutation in the alpha galactosidase A (α-Gal-A) gene (Xq22). The gene defect results in very low activity of the lysosomal enzyme α-Gal-A, with impaired metabolism of terminal α-D-galactosyl moieties. This abnormality impairs the conversion of globotriosylceramide (Gl_3) to lactosylceramide with intralysosomal accumulation of glycosphingolipids, particularly Gl_3.[1]

The first clinical symptoms of FD arise in childhood, typically between the ages of 4 and 10 years, and generally a few years later in girls than in boys.[2] With age, progressive damage to vital organ systems develops in both sexes leading to organ failure. End-stage renal disease and life-threatening cardiovascular or cerebrovascular complications limit life expectancy.[1]

Female heterozygotes have historically been erroneously described as "carriers." It is increasingly clear, however, that women with FD are also at high risk to develop major organ involvement and decreased quality of life.[3] The clinical spectrum among women ranges across a wide spectrum of severity

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that ranges from the "classic" severe phenotype (as seen in male patients) to a seemingly "oligosymptomatic" disease course.[3,4]

Aim

The aim of this study is to present observations from a series of brain magnetic resonance imaging (MRI) performed among a cohort of patients with FD and the relationship of imaging abnormalities with the presence of cardiovascular risk factors (CVRFs).

Methods

A total of 70 patients with FD (27 men and 43 women) were enrolled. In all cases, the diagnosis of FD was based on both enzymatic and molecular analyses. Clinical symptoms of FD such as acroparesthesias (neuropathic pain), renal (proteinuria), cardiac (left ventricular hypertrophy and/or arrhythmia), and ophthalmologic (cornea verticillata) involvement were assessed. Enzyme replacement therapy (ERT) status was recorded. The presence or absence of the following CVRFs was noted for all patients: current smoking, hypertension (systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg), diabetes mellitus (fasting blood sugar $\geq$ 126 mg/dL or hemoglobin $A_{1C} \geq 6.5\%$), dyslipidemia (serum low-density lipoprotein cholesterol $\geq$ 140 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL), and obesity (body mass index $\geq$ 30). All patients were recruited from different hospitals in Argentina. The study was approved by the local ethics committee, and all patients (and parents if applicable) provided written informed consent.

Magnetic Resonance Data Acquisition

All MRI scans were obtained on a 1.5-Tesla system with gradients of 40 mT/m (Magnetom Sonata; Siemens: Julián Segundo Agüero N° 2830, B1605EBQ, Vicente López, Provincia de Buenos Aires, Argentina). In addition to the acquisition of routine T1-weighted (repetition time [TR]/echo time [TE]: 600 ms/25 ms, matrix 256 × 256), proton density/T2-weighted (TR/TE1/TE2: 4500 ms/15 ms,100 ms, matrix 256 × 256), and fluid-attenuated inversion recovery-weighted (TR/TE 9000 ms/108 ms, slice thickness 6 mm, matrix 512 × 448) images and 3-dimensional (3D) magnetization-prepared rapid acquisition with gradient echo (TR/TE: 1900 ms/16 ms, matrix 512 × 512) data sets, we used a transverse diffusion-weighted, single-shot, spin-echo, echoplanar-based sequence with gradients along 6 noncollinear directions (TR/TE = 8000/105 ms, b = 0 and 1000 s/mm^2, matrix = 128 × 128, slice thickness 3 mm without gap, voxel size 1.8 × 1.8 × 3.0 mm) and 6 averages. The transverse slices were aligned to the anterior commissure–posterior commissure line and covered the whole brain saving 6 mm at the apex. Gradient echo sequence (GRE) and 5 mm axial sections were performed according to the following parameters: TR 700, TE 25, field of view 24 × 18, MTX 256 × 192, and NEX 1. The 3D time-of-flight was used for all patients.

Table 1. Prevalence of Signs/Symptoms and Cardiovascular Risk Factors in Both Sexes (n/%).

	Male (n = 27)	Female (n = 43)	*P*
Acroparesthesias	25/92.5	36/83.7	NS
Proteinuria	19/70.3	23/53.4	NS
LVH	6/22.2	15/34.8	NS
Cornea verticillata	23/85.1	41/95.3	NS
ERT	26/96.3	21/48.3	<.05
Blood hypertension	2/7.4	7/16.2	NS
Dyslipidemia	3/11.1	9/20.9	NS
Obesity	1/3.7	6/13.9	NS
Diabetes	0/0	0/0	NS

Abbreviations: ERT, enzyme replacement therapy; LVH, left ventricular hypertrophy; NS, not significant.

Magnetic resonance imaging evaluation included assessment for evidence of ischemia, hemorrhages (microbleeds), the presence of a "pulvinar sign," Chiari type I malformation, and vertebrobasilar dolichoectasia (VBD). Microbleeds were defined as a rounded or ovoid area showing marked and homogeneous signal loss on GRE, not located in sulcal areas, with diameters below 10 mm and devoid of T1-weighted or T2-weighted hyperintensity. For VBD, smoker criteria were used.[5]

Statistical Analysis

Data are expressed as mean ± standard error or proportions unless otherwise indicated. One-way analysis of variance was used for normally distributed variables and the Yate corrected chi-square test was used for categorical variables. Univariate and multivariate logistic regressions were used to identify those risk factors associated with the occurrence of the main outcome measure. A P value < .05 was used to define statistical significance.

Results

Participants available for study included 27 male and 43 female patients. The overall mean age was 32.6 ± 1.8 years. Among male and female patients, the mean age was 25.5 ± 2.2 and 37.0 ± 2.3, respectively. A total of 9 children were enrolled, including 6 boys (aged 7, 8, 9, 14, 15, and 15 years, respectively) and 3 girls (aged 8, 10, and 16 years, respectively). The ERT was indicated in 48.8% of female and 96.3% of male patients. Renal involvement was found in 61.8%, cardiac compromise in 30%, cornea verticillata in 90.2%, and acroparesthesias in 90.2% of patients. The prevalence of signs and symptoms in the study cohort is described in Table 1. Only 1 man was receiving renal replacement therapy (hemodialysis) at the time of study. Clinical neurologic examination showed no signs of central nervous system damage, and there was no history of stroke or transient ischemic attacks. For this reason, all cases of MRI evident brain ischemia or "microbleeds" were interpreted as reflecting "silent strokes." Brain MRI analysis found evidence of cerebral ischemic injury in 25.9% of men

Table 2. Brain MRI Findings in Both Sexes (n/%).

	Male (n = 27)	Female (n = 43)	*P*
Ischemias	7/25.9	13/30.2	NS
VBD	15/55.5	15/34.8	NS
Microbleeding	2/7.4	2/4.6	NS
Pulvinar sign	1/2.7	2/4.6	NS
Chiari type I	5/18.5	3/7	NS

Abbreviations: MRI, magnetic resonance imaging; NS, not significant; VBD, vertebrobasilar dolichoectasia.

Table 3. Logistic Regression Model.[a]

	β	CI (95%)	*P*
Dyslipidemia	.66	0.42-8.8	NS
Blood hypertension	1.89	0.44-30.9	NS
Obesity	.60	0.26-12.7	NS
Smoking	.39	0.43-5.1	NS

Abbreviations: CI, confidence interval; NS, not significant.
[a]Dependent variable: ischemia. $P = .07$.

and 30.2% of women. Vertebrobasilar dolichoectasia was diagnosed after imaging in 55.5% of men and 34.8% of women. Chiari type 1 malformation was found in 12.7% of images. Imaging from 4 patients demonstrated microbleeds and 3 demonstrated the pulvinar sign. The prevalence of MRI findings in both sexes is described in Table 2. The presence of at least 1 CVRF was reported in 40.7% of men and 55.8% of women, whereas the most common risk factor was smoking. In both sexes, findings of VBD were found at a younger age than the presence of ischemia. Vertebrobasilar dolichoectasia was present at a mean age of 26 years in men and at 43.8 years in women, whereas cerebral ischemic injury was found at a mean age of 36.6 and 50.5 years in men and women, respectively.

The logistic regression analysis adjusted for CVRF, using ischemia or VBD as a dependent variable, showed no statistically significant results (Tables 3 and 4). The presence of Fabry-related left ventricular hypertrophy was the single risk factor associated with the occurrence of VBD as well as brain ischemia ($P < .05$).

Discussion

Historically, the cerebral pathology of FD has been considered a secondary manifestation of a primary endotheliopathy.[6] However, involvement of smooth muscle cells (SMCs) in the vessel wall has also been demonstrated, suggesting a more complex pathogenesis.[7] Compromise of SMCs in the medial vessel layer is the result of the storage of globotriaosylceramide (Gb3) and the response to hypertrophic factors such as Lyso-Gl_3 and sphingosine-1 phosphate.[8] This last mechanism has been confirmed by in vitro studies of cardiomyocytes and SMCs in culture, where cell hypertrophy does not correlate with Gb3 accumulation due to 2% of the total left ventricular mass which is the direct result of substrate deposition.

Table 4. Logistic Regression Model.[a]

	β	CI (95%)	*P*
Dyslipidemia	.42	0.36-6.48	NS
Blood hypertension	.85	0.53-10.26	NS
Obesity	−.53	0.10-3.62	NS
Smoking	−.17	0.27-2.48	NS

Abbreviations: CI, confidence interval; NS, not significant
[a]Dependent variable: vertebrobasilar dolichoectasia. $P = .18$.

White matter lesions (WMLs) typically accumulate with increasing age. The presence of cerebral ischemias in MRI has already been reported in several case series from patients with FD. One review from the Fabry Outcome Survey (FOS) in 2005 reported that among 72 patients who received brain MRI, 58% showed WMLs.[9] Cerebrovascular events among patients in the FOS were reported at least as frequently in women as in men, with 11.1% of male and 15.7% of female patients having had a stroke or a transient ischemic attack. In a longitudinal MRI study of 50 patients with FD, all patients older than 55 years of age were found to have some degree of white matter change.[10] Fellgiebel et al[11] reported that the frequency and severity of WMLs were similar for both sexes, with a prevalence of 31% in male and 36% in female patients. In another study, the corresponding proportions were 27% (4 of 15) for women and 34% (11 of 32) for men.[12]

Reisin et al[13] described 36 adults with FD (14 men ± 31.2 years and 22 women ± 41.6 years) who were evaluated with MRI; 44% of them showed WMLs. Among the 16 patients with abnormal MRI, 12 were women. Similarly, our findings showed that silent WMLs are frequent in both sexes, despite the absence of overt clinical signs of cerebral disease. This study is further evidence confirming that women are not just carriers of FD and should be followed clinically and evaluated comprehensively to monitor for disease burden and progression.

Vertebrobasilar dolichoectasia is a potentially severe condition that may cause severe disability due to ischemic or compressive dysfunction in the posterior fossa. Vertebrobasilar dolichoectasia may not be readily recognized by many neurologists or radiologists owing to the "normal" variation in the tortuosity or diameter of the vertebral and basilar arteries in healthy individuals. The study of dolichoectasia has been hampered by a lack of standardized diagnostic criteria.[14] In 1986, Smoker and colleagues established criteria for assessing dolichoectasia in basilar arteries that were based on computed tomography angiography findings.[5] Smoker criteria use 3 quantitative measures of basilar artery morphology (see Table 5). The laterality score and bifurcation height (Figure 1) are surrogate measures for tortuosity and elongation, respectively, while basilar artery diameter represents the degree of dilatation (Figure 2). Since the first publication of smoker criteria, this diagnostic tool has been extended to include MRI and magnetic resonance angiography (MRA) measurements.

Table 5. Smoker Criteria for VBD.

Basilar artery diameter[a]
- 0 1.9-4.5 mm
- 1 ≥4.6 mm

Laterality ±
- 0 Midline throughout
- 1 Medial to the lateral margin of the clivus or dorsum sellae
- 2 Lateral to lateral margin of clivus or dorsum sellae
- 3 At the cerebellopontine angle

Height of bifurcation ±
- 0 At or below the dorsum sellae
- 1 Within the suprasellar cistern (1 cut above dorsum)
- 2 At the third ventricle floor (1 cut above suprasellar cistern)
- 3 Indenting and elevating the floor of the third ventricle (2 or more cuts above suprasellar cistern)

Abbreviation: VBD, vertebrobasilar dolichoectasia.
[a]Score of 1 indicates abnormality. ± Score ≥2 indicates abnormality.

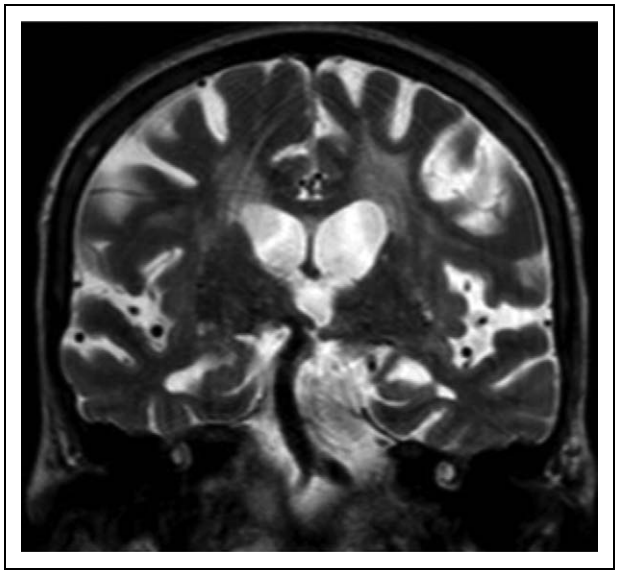

Figure 1. Vertebrobasilar dolichoectasia in 1 patient. Smoker criteria score 3 for height of bifurcation.

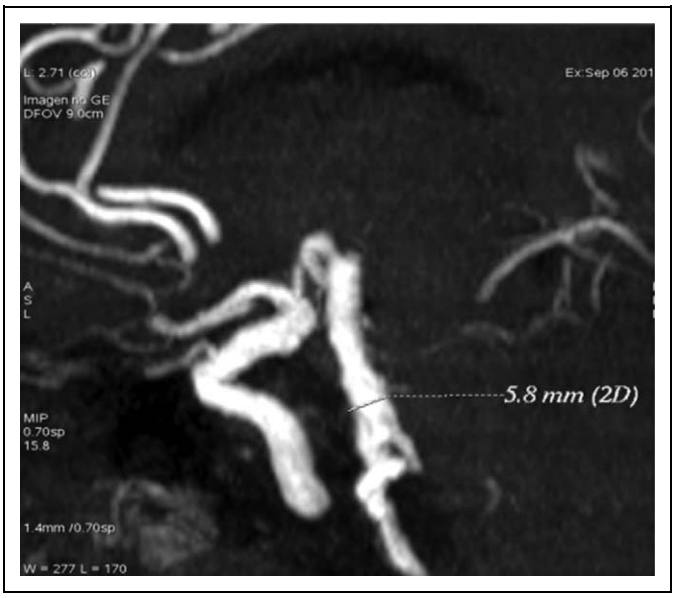

Figure 2. Vertebrobasilar dolichoectasia in 1 patient. Basilar artery diameter ≥ 4.6 mm.

However, although Smoker criteria can be used in some capacity to identify dolichoectatic vessels in the posterior circulation, these criteria cannot be used to assess this condition in other intracranial vessels.[14]

In our series, VBD was found in 55.5% of male and 34.8% of female patients. The accurate prevalence and incidence of VBD remain unknown in the general population. In the limited literature, the diagnostic frequency of VBD has been noted as 4.4% among 1440 MRA records,[15] 3.7% among 780 patients with posterior circulation ischemic stroke,[16] 6% among 381 autopsies of fatal stroke,[17] and 18.8% in 96 patients with isolated pontine infarction.[18] Pico et al[19] reported that intracranial arterial dolichoectasia, including VBD, is found in 12% of patients with stroke. It is important to emphasize that median age in all the previous series is more than 50 years. Our detection rate of VBD was far higher than these clinical and radiologic data; of additional note, the mean age of our study cohort was much lower.

While the French study of intracranial arterial dolichoectasia suggested that dilatative arteriopathy was associated with age, male sex, hypertension, and prior history of cardiovascular disease,[19] other reports have failed to demonstrate associations with diabetes, smoking, previous myocardial infarction, atherosclerosis, or traditional vascular risk factors.[20,21]

The role of atherosclerosis in dolichoectasia is unknown, and whether atherosclerosis is the inciting event or an innocent bystander remains to be determined. Our results did not demonstrate significant difference in relation to CVRFs and the presence or absence of VBD or cerebral ischemia. Currently, the different mechanisms involved in the cerebrovascular damage in FD have not demonstrated atherosclerosis as a major contributing risk factor. On the contrary, echo Doppler studies showed an increase in the intima–media thickness without the presence of atheriosclerotic plaques.[22,23] This finding has been reported in brain and coronary arteries in some autopsies.[24-26]

The primary cause of dolichoectasia seems to be aberrant vascular remodeling. Animal models indicate that acute augmentation of blood flow increases wall shear stress in blood vessels, dilates affected arteries, and stimulates endothelial cells to translate this mechanical stimulus into biochemical signals via tyrosine kinase and integrin signaling.[27] These signal transduction pathways activate gene transcription and affect downstream intracellular signaling cascades; ultimately, these biochemical processes lead to remodeling of the affected blood vessels so that endovascular pressures remain constant. Dilation is associated with a large increase in the levels of early growth response factor 1 in endothelial cells, and the expression of this transcription factor is closely linked

to the expression of metalloproteinases (MMPs),[28] especially MMP-9.[29] Evidence indicates that MMPs break down the elastic lamina, and degradation of this component of the arterial wall is thought to aid the migration of SMCs, residing in the tunica intima, to the stressed medial layer.[30] Levels of MMP-9 were significantly higher in patients with FD than in controls (1003.8 $\pm$ 337.8 ng/mL vs 576.7 $\pm$ 276.3 ng/mL, respectively), and there was a positive correlation between MMP-9 levels and Mainz Severity Score Index.[31]

Moore et al[32] found increased resting regional cerebral blood flow (rCBF) in FD using [^{15}O] H_2O and positron emission tomography without evidence of occlusive vasculopathy. At the same time, enhanced nitrotyrosine staining was observed in dermal and cerebral blood vessels. It has been shown that peroxynitrite can induce cerebral vasodilation with subsequent resistance to vasoconstriction by humoral mediators.[32] Such an effect could account for the hyperperfused cerebral circulation in FD. It is possible that the increased rCBF contributes to endothelial dysfunction and vessel wall dilation, resulting in an abnormal flow state increasing the incidence of WMLs.

Dolichoectasia can affect both the anterior and the posterior circulations, but the posterior circulation and the basilar artery are most frequently affected in FD. The posterior circulation has less sympathetic innervation than the anterior circulation.[33] This asymmetry in trophic support that the sympathetic nerves confer on the vessel walls may render the posterior circulation more susceptible to deformity upon exposure to increases in blood flow. Under normal conditions, the sympathetic tone of the cerebral arteries is probably minimal, but, under conditions of cerebrovascular stress, such as chronic elevation in blood perfusion, cerebral sympathetic activation might have a protective effect by shifting the static autoregulatory curve to the right.[34] If autoregulation is insufficient to maintain normal cerebral blood flow, the amount of blood flow into the cerebral vasculature will rise, causing higher static pressure on the cerebral vasculature. According to Laplace law, higher pressure and larger vascular radius will lead to higher wall tension. As a result, there is an increased risk of rupture to previously weakened vessel walls.[14,34] The first description of VBD in FD was in 1973,[35] soon after Mitsias and Levine[36] reported a review of 53 cases, and found elongated, ectatic, and tortuous vertebral and basilar arteries as the most common angiographic and pathologic features. Fellgiebel et al[37] reported results of MRI findings of 25 patients with FD, along with a control group. The principal finding of this study was that basilar artery diameter is clearly superior to WML load as well as global white matter diffusivity measurements (using diffusion tensor imaging) for the differentiation of FD from controls. Fellgiebel and colleagues demonstrated that, except for the anterior cerebral artery, all larger vessels of the circle of Willis were significantly dilated compared with those of age-matched healthy controls. However, the most evident large vessel pathology was clearly observed in the basilar artery. There are a few descriptions of histopathologic findings related to VBD and FD. Garzuly et al[38] presented 6 cases of VBD from 1 family; histologic studies in 1 case revealed storage material in SMCs of the wall of the basilar artery with typical lamellar ultrastructure. Finally, Okeda et al[39] described the autopsy findings in 1 patient, where all large arteries (diameter $\geq$ 1000 μm) showed slight intimal fibrous thickening sparsely mixed with SMCs, as well as adventitial fibrosis and lymphocytic infiltration, and nuclei of the medial SMCs were well preserved except for hydropic swelling of the cytoplasm due to intracellular glycolipid storage.

Chiari type I malformation is a rare condition characterized by a herniation of the cerebellar tonsils, which extend more than 5 mm below the foramen magnum. The prevalence has been reported to be lower than 0.24% in the literature. [40] Evidence suggesting that Chiari type I malformation is a genetic disorder comes from several sources, including family aggregation studies, twin studies, and an association with a number of other genetic conditions.[40] The prevalence of this malformation was 12.7% in our series, and to the best of our knowledge, this is the second time that this finding has been found in association with FD.[41] Our study is limited by its retrospective design and the lack of standardized diagnostic criteria for VBD and a control group.

Conclusion

Our results have demonstrated cerebrovascular involvement before the third decade in many patients with FD. This study is further evidence confirming that women are not just carriers of FD and should be followed clinically and evaluated comprehensively to monitor for disease burden and progression. Although silent brain ischemias in MRI should be included as a key feature for the diagnoses of FD, VBD is an earlier and frequent sign.

Declaration of Conflicting Interests

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References

1. Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Bases of Inherited Disease*. 8th ed. New York: MacGraw-Hill; 2001:3733-3774.
2. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Mol Genet Metab*. 2008;93(2):112-128.
3. Germain D. Fabry Disease. *Orphanet J Rare Dis*. 2010;5:30.
4. MacDermot K, Holmes A Miners H. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet*. 2001;38(11):769-775.
5. Smoker WR, Corbett JJ, Gentry LR, Keyes WD, Price MJ, McKusker S. High-resolution computed tomography of the basilar artery: 2. vertebrobasilar dolichoectasia: clinical– pathologic correlation and review. *AJNR Am J Neuroradiol*. 1986;7(1): 61-72.

6. Ruiter M, Pompen AWM, Wijers HJG. Über internmedizinisch e und pathologisch-anatomisch e Befunde bei Angiokeratome corporis diffusum (Fabry). *Dermatol*. 1947;94:1-12.
7. Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE. Vasculopathy in patients with Fabry disease: current controversies and research directions. *Mol Genet Metab*. 2010;99(2):99-108.
8. Brakch N, Dormond O, Bekri S, et al. Evidence for a role of sphingosine-1 phosphate in cardiovascular remodelling in Fabry disease. *Eur Heart J*. 2010;31(1):67-76.
9. Mehta A, Ginsberg L. Natural history of the cerebrovascular complications of Fabry disease. *Acta Paediatr Suppl*. 2005;94(447):24-27.
10. Crutchfield KE, Patronas NJ, Dambrosia JM, et al. Quantitative analysis of cerebral vasculopathy in patients with Fabry disease. *Neurology*. 1998;50:1746-1749.
11. Fellgiebel A, Müller MJ, Mazanek M, Baron K, Beck M, Stoeter P. White matter lesion severity in male and female patients with Fabry disease. *Neurology*. 2005;65(4):600-602.
12. Ginsberg L, Manara R, Valentine AR, Kendall B, Burlina AP. Magnetic resonance imaging changes in Fabry disease. *Acta Paediatr Suppl*. 2006;95:57-62.
13. Reisin RC, Romero C, Marchesoni C, et al. Brain MRI findings in patients with Fabry disease. *J Neurol Sci*. 2011;305(1-2):41-44.
14. Gutierrez J, Sacco RL, Wright CB. Dolichoectasia an evolving arterial disease. *Nat Rev Neurol*. 2011;7(1):41-50.
15. Ubogu E, Zaidat O. Vertebrobasilar dolichoectasia diagnosed by magnetic resonance angiography and risk of stroke and death: A cohort study. *J Neurol Neurosurg Psychiatry*. 2004;75(1):22-26.
16. Kumral E, Kisabay A, Ataç C, et al. The mechanism of ischemic stroke in patients with dolichoectatic basilar artery. *Eur J Neurol*. 2005;12(6):437-444.
17. Pico F, Labreuche J, Seilhean D, Duyckaerts C, Hauw JJ, Amarenco P. Association of small vessel disease with dilatative arteriopathy of the brain: Neuropathologic evidence. *Stroke*. 2007;38(4):1197-1202.
18. Kwon HM, Kim J, Lim J-S, Park JH, Lee SH, Lee YS. Basilar artery dolichoectasia is associated with paramedian pontine infarction. *Cerebrovasc Dis*. 2009;27(2):114-118.
19. Pico F, Labreuche J, Touboul PJ, Leys D, Amarenco P. Intracranial arterial dolichoectasia and small-vessel disease in stroke patients. *Ann Neurol*. 2005;57(4):472-479.
20. Passero S, Filosomi G. Posterior circulation infarcts in patients with vertebrobasilar dolichoectasia. *Stroke*. 1998;29(3):653-659.
21. Pico F, Labreuche J, Cohen A, Touboul PJ, Amarenco P. Intracranial arterial dolichoectasia is associated with enlarged descending thoracic aorta. *Neurology*. 2004;63(11):2016-2021.
22. Boutouyrie P, Laurent S, Laloux B, Lidove O, Grunfeld JP, Germain DP. Arterial remodelling in Fabry disease. *Acta Paediatr Suppl*. 2002;91(439):62-66.
23. Barbey F, Brakch N, Linhart A, et al. Increased carotid intima-media thickness in the absence of atherosclerotic plaques in an adult population with Fabry disease. *Acta Paediatr Suppl*. 2006; 95(451):63-68.
24. Schiffmann R, Rapkiewicz A, Abu-Asab M, et al. Pathological findings in a patient with Fabry disease who died after 2.5 years of enzyme replacement. *Virchows Arch*. 2006;448(3):337-343.
25. Suzuki O, Abe M. An autopsy case of Fabry's disease with cardiac manifestations. *J Clin Exp Hematop*. 2009;49(2): 121-123.
26. Sheppard MN, Cane P, Florio R, et al. A detailed pathologic examination of heart tissue from three older patients with Anderson-Fabry disease on enzyme replacement therapy. *Cardiovasc Pathol*. 2010;19(5):293-301.
27. Chen KD, Li YS, Kim M, et al. Mechanotransduction in response to shear stress. Roles of receptor tyrosine kinases, integrins, and Shc. *J Biol Chem*. 1999;274(26):18393-18400.
28. Sho E, Sho M, Singh TM, et al. Arterial enlargement in response to high flow requires early expression of matrix metalloproteinases to degrade extracellular matrix. *Exp Mol Pathol*. 2002; 73(2):142-153.
29. Tronc F, Mallat Z, Lehoux S, Wassef M, Esposito B, Tedgui A. Role of matrix metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. *Arterioscler Thromb Vasc Biol*. 2000;20(12):E120-E126.
30. Lehoux S, Castier Y, Tedgui A. Molecular mechanisms of the vascular responses to haemodynamic forces. *J Intern Med*. 2006;259(4):381-392.
31. Shah JS, Hughes DA, Tayebjee MH, MacFadyen RJ, Mehta AB, Elliott PM. Extracellular matrix turnover and disease severity in Anderson-Fabry disease. *J Inherit Metab Dis*. 2007;30(1): 88-95.
32. Moore DF, Scott LT, Gladwin MT, et al. Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation*. 2001;104(13):1506-1512.
33. Dunatov S, Antoncic I, Bralic M. Hemodynamic changes in the posterior cerebral circulation triggered by insufficient sympathetic innervation–cause of primary intracerebral hemorrhage? *Med Hypotheses*. 2011;76(5):668-669.
34. Edvinsson L. Neurogenic mechanisms in the cerebrovascular bed. *Acta Physiol Scand (Suppl)*. 1975;427:1-35.
35. Kahn P. Anderson-Fabry disease: a histopathological study of three cases with observations on the mechanism of production of pain. *J Neurol Neurosurg Psychiatry*. 1973;36(6):1053-1062.
36. Mitsias P, Levine SR. Cerebrovascular complications of Fabry's disease. *Ann Neurol*. 1996;40(1):8-17.
37. Fellgiebel A, Keller I, Marin D, et al. Diagnostic utility of different MRI and MR angiography measures in Fabry disease. *Neurology*. 2009;72(1):63-68.
38. Garzuly F, Maródi L, Erdös M, et al. Megadolichobasilar anomaly with thrombosis in a family with Fabry's disease and a novel mutation in the alpha-galactosidase A gene. *Brain*. 2005;128(9): 2078-2083.
39. Okeda R, Nisihara M. An autopsy case of Fabry disease with neuropathological investigation of the pathogenesis of associated dementia. *Neuropathology*. 2008;28(5):532-540.
40. Milhorat TH, Chou MW, Trinidad EM, et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. *Neurosurgery*. 1999;44(5):1005-1017.
41. Germain DP, Benistan K, Halimi P. Chiari type I malformation in four unrelated patients affected with Fabry disease. *Eur J Med Genet*. 2006;49(5):419-425.