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Fabry disease in children: correlation between ocular manifestations, genotype and systemic clinical severity

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ABSTRACT

Background/aims: Fabry disease is an X-linked lysosomal disorder associated with severe multi-organ failure and premature death. This study aims to determine the prevalence of ophthalmic manifestations in children with the condition and investigate the correlation with genotype and systemic disease severity.

Methods: The records of 26 children from 18 pedigrees with Fabry disease undergoing regular ophthalmic and systemic examination were reviewed. All pedigrees underwent *GLA* gene sequencing to determine genotype. Correlations between ocular and systemic phenotype and genotype were investigated.

Results: Corneal verticillata occurred in 50% of the children in this study (95% confidence interval 29-79%). Children with ophthalmic manifestations were more likely to have loss-of-function *GLA* mutations (p=0.003). Retinal vascular tortuosity was seen in seven children (27%) all of whom had systemic symptoms suggestive of autonomic neuropathy, such as diarrhoea and syncope. These symptoms seemed less prevalent in children without retinal vascular changes, although this did not reach statistical significance (p=0.134).

Conclusion: Ophthalmic manifestations of Fabry disease are common, even in young children, with loss-of-function *GLA* gene mutations. Although the limited sample size possibly prevented statistical significance, systemic symptoms of autonomic neuropathy often coexist with retinal vascular changes and may share the same pathogenesis.

INTRODUCTION

Fabry disease (OMIM 301500) is an X-linked inherited lysosomal storage disorder associated with severe multi-organ dysfunction and premature death.[1,2] Fabry disease is hemizygous in males and heterozygous in females, but both genders can be severely affected, although the disease is usually slower to progress and is more variable in females.[2-6]The condition is rare, with an estimated incidence of up to1 in 40,000 male live births.[7] *GLA* gene mutations reduce the activity of α-galactosidase A, resulting in globotriaosylceramide (Gb_3) deposition in a variety of cells, including those of the kidney, autonomic and cardiovascular system, as well as the cornea.[1,2,8]

Ophthalmologists are a key group in the identification and referral of patients with Fabry disease. Eye examinations are relatively simple and represent a non-invasive method for assisting in the clinical diagnosis of patients with potential Fabry disease.[9,10] Ophthalmological manifestations of Fabry disease result from the progressive deposition of glycosphingolipids in various ocular structures, although these do not usually cause ocular symptoms or visual impairment.[9] The most frequently reported eye abnormalities are corneal verticillata (corneal opacities), conjunctival and retinal vascular abnormalities (vessel dilatation and tortuosity) and lens opacities (Figures 1 and 2).[9,10]. Ophthalmological signs are usually present in children before serious systemic symptoms develop.[11]

The relative rarity and variability of the condition make diagnosis difficult and many patients suffer from delayed diagnosis or misdiagnosis for years. In the Fabry Outcome Survey (FOS), of 366 patients in all age groups, the mean time between onset of symptoms and diagnosis was 13 years for men and 16 years for women.[12] In children (< 18 years), there was an approximate 3-year delay between symptom onset and diagnosis.[11] Accurate and rapid diagnosis of Fabry disease, particularly in children, is urgently needed now that effective treatment with enzyme replacement therapy (ERT) is available. Replacement α-

galactosidase A (agalsidase alfa: Replagal, Shire Human Genetic Therapies, agalsidase B: Fabrazyme, Genzyme Europe) therapy has been demonstrated to clear tissue globotriaosylceramide and to improve clinical endpoints, including stabilizing renal function, reducing pain, improving cardiac structure and function, improving gastrointestinal symptoms and stabilizing mild-to-moderate hearing loss.[13-17] It may now therefore be possible to halt and even reverse the progress of Fabry disease before irreversible organ damage occurs.

Symptoms of Fabry disease, particularly acroparaesthesiae (numbness, pain or tingling in the extremities) and altered temperature sensitivity, altered bowel habits and abdominal pain, together with angiokeratoma, hypohidrosis, lethargy, and ophthalmological and auditory signs usually present in childhood (< 10 years), with life-threatening renal, cardiac or neurological complications in adulthood.[1,2,7,11,12] Resultant renal failure, cardiomyopathy and cerebrovascular disease lead to premature death, on average 15 years earlier in women and 20 years earlier in men compared with the general population.[1,2] To extend these studies in children, we investigated the relationship between genotype, ophthalmic phenotype and the severity of the systemic manifestations in children with the diagnosis of Fabry disease attending our centre. The aim was to assess whether ocular involvement is associated with a more severe systemic phenotype in affected children, and whether this is related to genotype.

MATERIALS AND METHODS

The Paediatric Metabolic Unit at Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's Hospital) holds a database of children with Fabry disease seen in the Department. All pedigrees are genotyped by *GLA* gene sequencing and the children have annual ophthalmic and biannual systemic examinations.

We analysed the first recorded ophthalmic examination and clinical findings for eight different systems for children with Fabry disease undergoing their biannual review.

The ophthalmic examination included: visual acuity assessment, refraction and slit-lamp examination for conjunctival and retinal vascular tortuosity, corneal haze/verticillata and lens opacities. Anterior segment and retinal photography were performed. Retinal vascular tortuosity was assessed by a single experienced ophthalmologist (LEA) studying the calibre and directness of path of vessels using digital retinal photographs.

Systemic examination included a general assessment performed by a single experienced metabolic paediatrician (UR) with specific questioning regarding symptoms, and full physical examination. Radiological evaluation of cardiac, renal and neurological function, and audiometry were performed annually at the same centre by experienced personnel.

ERT is considered by the paediatric metabolic team if a child has uncontrolled pain leading to a need to alter lifestyle, or pain that interferes with quality of life and has one or more of the following manifestations: severe asthenia, lethargy, gastroenterological symptoms such as pain, vomiting or altered bowel habit, abnormal MRI, episodic vertigo, intra-ventricular conduction defects, and/or poor growth that cannot be accounted for by another cause.[18]

Systemic phenotyping was determined by multi-system history, examination and laboratory results. Ocular and systemic phenotypes were correlated with genotype, gender, age, systemic manifestations of the disease and commencement of ERT.

RESULTS

We reviewed data from 26 children from 18 pedigrees (12 hemizygous boys of median age 5 years and 14 heterozygous girls of median age 11 years (range 1-

15 years). Seven children (3 boys and 4 girls, median age 8 years range 3-15 years) were already receiving ERT at the time of the first ophthalmic examination.

Molecular Genetic Results

Thirteen different *GLA* gene mutations were identified (Table 2). Loss-of-function mutations affected 17 children; mutations predicted to give residual enzymatic activity affected nine children.

Table 1. *GLA* genotypes detected in patients with Fabry disease

Mutation type	Predicted effect	*N* = 26	Genotype (*n*)
Nonsense	Loss-of-function	5	p.W209X (2) p.R301X (2) p.R227X (1)
Deletion	Loss-of-function	1	c.1088delG (1)
Missense	Predicted loss-of-function	11	p.R49S (4) p.N298H (1) p.P205T (1) p.C520T (2) c.902G>A (1) c.319C>T (1) p.T950C (1)
Missense	Predicted residual activity	9	p.N215S (7) p.A143T (2)

Ophthalmic Examination

Thirteen of the 26 children (50%) were found to have corneal verticillata, the youngest being a girl 2 years of age (95% confidence interval 29-79%). None had severe corneal manifestations and, of the 7 children with moderate changes, 6

were heterozygous females. The median age range of the children with verticillata was 8.1 years (range 2-15 years) whilst that of the group without verticillata was 10.9 years range (1-15 years).

Seven children (27%) had evidence of retinal vascular tortuosity, the youngest being 4 years of age. One child of 5 years of age had mild spoke cataracts but no patient had conjunctival vascular tortuosity.

All 7 children (4 girls, 3 boys) with retinal vascular tortuosity had neurological (asthenia / temperature insensitivity / hypohydrosis / syncope) and gastrointestinal symptoms (nausea / vomiting / diarrhoea), and 5 had cardiac symptoms (chest pain, trivial valve disease including triscupid and mitral regurgitation) and auditory signs (hearing impairment / tinnitus / vertigo) (Table 1). Of the other 19 children, 13 had gastrointestinal symptoms, 11 auditory problems, 8 had neurological symptoms and 10 had cardiac symptoms (Fisher's exact test $p=0.134$).

Table 2. Systemic features in children with retinal vascular tortuosity. (* denotes patients on ERT)

Age(yrs)	Genotype	Neurological	Gastrointestinal	Cardiac	Renal	Auditory
13.5*	1088delG	+	+	-	+	+
12.8	R301X	+	+	-	-	-
8.8*	R49S	+	+	+	-	+
4.0	P205T	+	+	+	-	+
15.0*	C520T	+	+	+	-	+
13.5*	C520T	+	+	+	-	+
14.7	R301Q	+	+	+	-	-

Systemic Examination

The most frequent systemic manifestations of Fabry disease were gastrointestinal (n = 20 patients) neurological (n = 14) and cardiac (n = 15) and auditory (n = 16) abnormalities. All other abnormalities were reported for less than 5 patients.

Ophthalmic manifestations were found in 76% of patients predicted to have no enzyme function and in only 1 patient with a genotype predicted to give some residual enzyme function (Table 3) (Fisher's exact test p=0.03). However, patients predicted to have some residual enzyme function had a similar prevalence of neurological, gastrointestinal and auditory symptoms as those with

loss-of-function mutations. Cardiac and renal symptoms were actually more common in the group with predicted residual enzyme function.

Table 3. Comparison of frequency of systemic features with genotype groups.

Predicted enzyme activity	*N*=26	Eye signs	Neurological	Gastrointestinal	Cardiac	Renal	Auditory
None	17	13 (76%)	10 (59%)	13 (76%)	8 (47%)	2 (12%)	10 (59%)
Residual	9	1 (11%)	5 (55%)	7 (78%)	7 (78%)	2 (22%)	6 (67%)

DISCUSSION

Fabry disease is a rare condition and, in this context, the 26 children and adolescents included in the current study are a significant cohort of young patients. The data from the current study agree with and add to the literature on reported ophthalmological manifestations of Fabry disease.

The FOS study demonstrated that the most common ocular manifestation of Fabry disease is corneal verticillata (occurring in approximately 70% of adult patients) and that its presence does not correlate with Fabry illness severity measured by disease progression, renal function and cardiac size.[10] In our study, corneal verticillata were seen in 50% of children studied (95% CI 29-79%), the youngest being a 2 year old heterozygous female. The children with verticillata did not tend to be older than the group without corneal changes.

The FOS study showed a prevalence of retinal vascular tortuosity of 49% in males and 22% of females and of Fabry cataract in 23% males and 10%

females; these features are thought to become more common with age.[10,11] Vessel tortuosity on its own is not diagnostic for Fabry disease but has been recognised as being predictive of more severe illness severity.[10,19] Retinal vascular tortuosity was present in 27% of the children in this study and was identified in a child of only 4 years of age. Whereas all the children who had evidence of retinal vascular tortuosity also had gastro-intestinal and neurological symptoms, a minority of those without retinal vascular changes manifested these symptoms of autonomic neuropathy. This did not meet statistical significance (Fisher's exact test p=0.134) in our study, possibly due to the small sample size, but does hint of a possible association between these features.

The pathophysiology of retinal vascular dilatation and tortuosity in Fabry disease is not fully understood. Autonomic neuropathy has been implicated as the cause of the diarrhoea, hypohydrosis and syncope seen in Fabry patients.[20] Autonomic neuropathy secondary to diabetes has been reported to cause both bulbar and retinal vascular dilatation and tortuosity, as has cervical sympathectomy, due to the detrimental effect on retinal vascular auto-regulation.[21-24] Retinal and bulbar conjunctival vessel dilatation and tortuosity are therefore likely to be a marker for autonomic neuropathy in Fabry patients.

Loss-of-function mutations affected approximately two-thirds of patients in the present study, while mutations predicted to give residual enzymatic activity affected about one-third of patients. Although ophthalmic findings were much more commonly associated with loss-of-function mutations (Fishers exact test p=0.03), the prevalence of cardiac and renal systemic manifestations was higher in genotypes with predicted residual enzymatic activity.

Although the absence of ophthalmic signs does not appear to correlate with milder systemic disease, those children with absent eye signs but known systemic manifestations of Fabry disease may be predicted to have a missense mutation causing residual enzyme activity rather than a loss-of-function mutation.

Ophthalmological examination including slit-lamp examination should be conducted in young patients with symptoms of Fabry disease (e.g. neuropathic pain, diarrhoea, tinnitus, vertigo). Once other causes of corneal verticillata (such as long term therapy with choroquine or amiodarone) have been excluded, the presence of cornea verticillata is diagnostic of Fabry disease. The additional presence of retinal vascular tortuosity indicates that autonomic neuropathy is likely and these patients may already have potentially severe systemic manifestations.

Serial ophthalmological examinations may also be useful in monitoring the response to ERT. Quantification of severity of corneal verticillata is currently highly subjective.[10] The presence of retinal vascular dilatation and tortuosity was assessed subjectively in this study and generally this has been shown to be a reliable form of assessment. [25] To date there have been no large population studies determining the prevalence of retinal vascular dilatation and tortuosity in the normal population although it is felt that these changes, even in childhood, may be a potential predictor for vascular disease in later life. [25] The development of image analysis software such as Retinal Image multiScale Analysis (RISA) may allow more accurate identification and monitoring of vascular changes during therapy.[26]

CONCLUSION

Ophthalmic signs of Fabry disease are common in even young children with loss-of-function *GLA* mutations. Children with conjunctival and retinal vascular dilatation and tortuosity are likely to have associated severe systemic disease, and this may be an indicator of autonomic neuropathy.

The ocular symptoms of Fabry disease are generally trivial and few patients will attend an ophthalmologist spontaneously. It is important that optometrists and ophthalmologists are aware of the ocular features of Fabry disease and that

paediatricians consider this diagnosis in children with neuropathic pain and gastrointestinal symptoms. Slit-lamp examination provides a simple, quick, inexpensive and painless screening test for children with symptoms suggestive of Fabry disease.

Early recognition of Fabry disease will ensure that therapies including ERT are considered at an early stage of disease progression and we suggest that children with suspected Fabry disease are referred to a specialist centre for further evaluation and consideration of such treatment.

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References

1. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet 2001;38:750–60.

2. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. J Med Genet 2001;38:769–75.

3. Whybra C, Kampmann C, Willers I et al. Anderson–Fabry disease: clinical manifestations of disease in female heterozygotes. J Inherit Metab Dis 2001;24:715–24.

4. Whybra C, Miebach E, Mengel E et al. A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. Genet Med 2009;11:441-9

5. Galanos J, Nicholls K, Grigg L et al. Clinical features of Fabry disease in Australian patients. Intern Med J 2002;32:575–84.

6. Kampmann C, Baehner F, Whybra C et al. Cardiac manifestations of Anderson-Fabry disease in heterozygous females. J Am Coll Cardiol 2002;40:1668–74.

7. Meikle PJ, Hopwood JJ, Clague AE et al. Prevalence of lysosomal storage disorders. JAMA 1999;281:249–54.

8. Branton MH, Schiffmann R, Sabnis SG et al. Natural history of Fabry renal disease: influence of α-galactosidase A activity and genetic mutations on clinical course. Medicine 2002;81:122–38.

9. Sodi A, Ioannidis A, Pitz S. Ophthalmological manifestations of Fabry disease. In: Metha A, Beck M, Sunder-Plassmann G,eds. Fabry disease. Perspectives from 5 years of FOS. Oxford Pharmagenesis Ltd, Oxford, UK;2006:249–61.

10. Sodi A, Ioannidis AS, Mehta A et al. Ocular manifestations of Fabry's disease: data from the Fabry Outcome Survey. Br J Ophthalmol 2007;91:210–4.

11. Ramaswami U, Whybra C, Parini R et al. Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. Acta Paediatr 2006;95:86–92.

12. Mehta A, Ricci R, Widmer U et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004;34:236–42.

13. Beck M, Ricci R, Widmer U et al. Fabry disease: overall effects of agalsidase alfa treatment. Eur J Clin Invest 2004;34:838-44

14. Schaefer RM, Tylki-Szmanska A, Hilz MJ. Enzyme replacement therapy for Fabry disease: A systematic review of available evidence. Drugs 2009;69:2179-205

15. Hoffmann B, SchwartzM, Mehta A et al. Gastro-intestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol 2007;5:1447-53

16. Hughes DA, Elliott PM, Shah J et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo controlled trial of agalsidase alfa. Heart 2008;94:153-8

17. West M, Nicholls K, Mehta A et al. Agalsidase alfa and kidney dysfunction in Fabry disease. J Am Soc Nephrol 2009;20:1132-9

18. DA Hughes, U Ramaswami, P Elliott et al. Guidelines for the diagnosis and management of Anderson-Fabry Disease. *http://www.ncg.nhs.uk/documents/lsd_guidelines_for_anderson-fabry_disease-010805.pdf*

19. Fumex-Boizard L, Cochat P, Fouilhoux A et al. Relation between ocular manifestations and organ involvement in ten patients with Fabry disease. J Fr Ophtalmol 2005;28:45–50.

20. Laaksonen SM, Roytta M, Jaaskelainen SK et al. Neuropathic symptoms and findings in women with Fabry disease. Clin Neurophysiol 2008;119:1365-72

21. Lanigan LP, Birke R, Clark CV et al. The effect of cervical sympathectomy on retinal vessel responses to systemic autonomic stimulation. Eye 1990;4:181-9

22. Lanigan LP, Clark AV, Allawi J et al. Responses of retinal circulation to systemic autonomic stimulation in diabetes mellitus. Eye 1989;3:39-4

23. Tesfaye S, Malik R, Harris N et al. Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glycaemic control. Diabetologia 1996;39:329-35

24. Owen CG, Newsom RS, Rudwick AR et al. Diabetes and the tortuosity of vessels of the bulbar conjunctiva. Ophthalmology 2008;115(6):e27-32

25. Owen CG, Rudnicka AR, Mullen R et al. Assisted Image Analysis of the Retina (CAIAR) program. IOVS 2009;50:1552-5783

26. Gelman R, Jiang L, Yunling et al. Plus disease in retinopathy of prematurity: Pilot study of computer-based and expert diagnosis. J AAPOS 2007;11:532-540

LEGENDS

(Note to publisher left figure is Figure 1, right figure is figure 2)

Figure 1: slit-lamp photograph of corneal verticillata

Figure 2: Fundus photograph of moderate retinal vascular tortuosity