International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (875-880), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Clinical Features and Complications of Fabry Disease; Systematic Review

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Abstract: **Fabry disease (FD) is a rare X-linked l ysosomal storage condition. The disease is defined by shortage of the lysosomal enzyme α-galactosidase A. This study aims to improve our understanding of the clinical manifestation of patients with Fabry disease and to discuss the complications that can affect patient's life from several aspects. The following electronic databases have been searched via OvidSP: Medline Embase and The Cochrane Central Register of Controlled Trials, has been searched as well for all published studies until the December 2016.The search terms used were: Fabry disease, complications, clinical features, pain measurement, and their synonyms, Mesh terms (Medline) and headings (Embase). Fabry disease is uncommon and provides with varied symptoms in childhood and medical diagnosis is frequently delayed. Physicians needs to be familiar with early signs and symptoms of Fabry disease, which should be thought about in the differential diagnosis when a young patient presents with several non-specific or unusual but reoccurring or episodic signs, particularly inexplicable neuropathic pain, gastrointestinal signs, workout tiredness, intolerance and hypohidrosis.**

Keywords: **Fabry disease (FD), pain measurement, clinical features, synonyms, (Medline), hypohidrosis.**

1. INTRODUCTION

Fabry disease (FD) is a rare X-linked l ysosomal storage condition. The disease is defined by shortage of the lysosomal enzyme α-galactosidase A [(1)]. This results in a systemic build-up of globotriaosylceramide (Gb3) and associated glycosphingolipids in lysosomes in cells throughout the body. The occurrence of FD is approximated at 1:40.000--170.000 live births [(1,2,3)] although recent newborn and high-risk group screening research studies suggested that the occurrence of non-classical FD might be much higher than previously thought [(4,5)]. Phenotypically, FD can be differentiated in the more serious classical kind of FD, mainly impacting males, and a non-classical type, more prominent in males with recurring enzyme activity. Although women can be as significantly affected as male patients with classical FD, the majority of them have a more variable and attenuated phenotype and are therefore better characterised as non-classical patients [(6)].

Early symptoms in classically affected male and female patients consist of angiokeratoma, anhydrosis, neuropathic pain, intestinal symptoms and microalbuminuria. Later in life, progressive renal failure, cardiac arrest and stroke normally happen. In non-classically affected male patients and most females, the disease presents with a more attenuated and variable disease course [(7,8,9,10)]. The reduced life span and the morbidity of Fabry patients are strongly related to the degree of end-organ damage.

Patients who struggle with FD have a lower quality of life (QoL) compared with healthy people. Neuropathic pain and anhidrosis are predictors of reduced QoL, presumably as a marker of more extreme disease [(3)]. Disease symptoms in female heterozygotes have been reported, but are thought about to be generally mild and unusual [(11)]. Asymptomatic corneal dystrophy (cornea verticillata and posterior lenticular cataract) exists in about 70% and is useful for heterozygote detection. About 30% of females have minimal angiokeratomas and <10% have infrequent attacks of neuro- pathic discomforts [(11)]. Nevertheless, female heterozygotes with extreme and early cerebrovascular disease, strokes, and renal failure have actually been docu- mented, however these serious manifestations were estimated to occur in just 1% [(11)]. Due to the fact that this is an X connected condition, these serious manifesta- tions in females were described by skewed X inactivation [(12)].

Objectives:

This systematic review provides an overview of the literature with the aim to improve our understanding of the clinical manifestation of patients with Fabry disease and to discuss the complications that can affect patient's life from several aspects.

2. METHODS

The following electronic databases have been searched via OvidSP: Medline Embase and The Cochrane Central Register of Controlled Trials, has been searched as well for all published studies until the December 2016.The search terms used were: Fabry disease, complications, clinical features, pain measurement, and their synonyms, Mesh terms (Medline) and headings (Embase). limits were applied for language therefore only English language articles were included involving human subject only. The title and abstract of all articles obtained by the search were screened to identify studies where complication and clinical manifestation of patients with FD was studied. Reference lists of identified papers were hand searched for additional relevant citations.

3. RESULTS & DISCUSSION

- ***Clinical manifestations in children with Fabry disease:***

Fabry disease is a progressive multisystem disorder. The early symptoms and indications of classical Fabry disease generally present in childhood however the main disease process begins throughout early fetal development. There is histopathological evidence of GL3 accumulation in renal, liver and myenteric plexus cells in impacted males' fetuses. Corneal whorls have actually been identified in a 22-week male fetus [13,14,15]. Males experience symptoms at an earlier age and at a higher prevalence than women. Review of the Fabry Registry information showed the mean age of sign start in males was 6 and 9 years in women. The very first medical presentation at a typical age of 7 years in males was episodic neuropathic pain providing with burning pain of the feet and hands referred to as acroparaesthesia taking place in 59% of males and 41% of women at a mean age of 9 years. Reoccurring intestinal symptoms were the 2nd most typical feature in 27% with typical age of beginning in males of 5 and 9.5 years in females. Hypohidrosis and heat intolerance are likewise typical in the early stage of the disease [16]. Although not life-threatening these signs influence on the health, quality of life and function of afflicted children.

The most serious complications of Fabry disease emerge in the adult years and include end phase kidney failure, cerebrovascular occasions such as strokes, and progressive cardiomyopathy, arrhythmias and valvular disease and sudden death. Despite being X-linked, Fabry disease affects women. Signs in female heterozygotes may be more variable, however can be of the exact same seriousness as in males [17,18]. There is a large range of inter and intrafamilial variability of medical features.

- ***Neurological manifestation and complications in patients with fabry disease:***

Neuropathic pain experienced by young patients with Fabry disease manifests as chronic acroparaesthesia superimposed by acute attacks of Fabry pain crisis. These signs show damage to little fibers in the peripheral and free nervous systems as a result of build-up of glycosphingolipids [19]. Acroparaesthesia is frequently described by patients as a persistent, unpleasant, tingling, burning feeling in the hands and feet whilst a pain crisis is an episode of severe, painful pain, starting in the extremities and radiating proximally. The pain is typically precipitated by quick modifications in core body temperature due to fever, workout, health problem or tension, sudden exposure to cold, modifications in humidity or tiredness. Acroparaesthesia has actually been reported in children as young as 2 years [17]. Fabry pain crises might likewise manifest as intense stomach pain. Other signs connected to dysfunction of the autonomic nervous system observed in Fabry patients include hypo- or anhidrosis, temperature level and exercise intolerance and impaired intestinal motility [20]. Early cerebral participation has been reported in an asymptomatic 8-year-old young boy with white matter lesions shown by brain magnetic resonance imaging [21].

- ***Dermatological menfestation of FD patients:***

Angiokeratoma looking like small, raised, non-blanching dark-red spots are the trademark of Fabry disease although not specific for the condition. Angiokeratoma can be idiopathic or related to other disorders. Scattered angiokeratoma are typically located in the lower trunk and genital region, however might also be present on the palms, around the mouth,

lips and umbilicus [22]. Irregular free nerve function and seepage of the sweat glands is thought to result in hyperhidrosis, heat and workout intolerance. In heats patients may experience flushing, beginning of neuropathic pain, headache, heat or fatigue stroke whilst in the cold they may experience pain or tingling in the extremities [22].

- ***Ophthalmological symptoms in patients with FD:***

Vortex keratopathy or cornea verticillata is the most frequent ocular sign in Fabry disease occurring in over 70% of females and males consisting of children making ophthalmological examination an useful tool for early diagnosis of Fabry disease [21]. It is very rare in individuals without Fabry disease. The presence of cornea verticillata has actually been reported in a 6-month old child and in a fetus [23]. Cornea verticillata are golden brown or gray, usually bilateral, opacities that branch off from a main whorl throughout the inferior cornea. Retinal vessel tortuosity and cataracts have also been reported and happen more often in males. The existence of vascular tortuosity has actually been correlated with disease severity in children and may represent a more severe phenotype [22]. Ophthalmological indications might be present in children prior to the beginning of other indications or symptoms and do not typically lead to visual impairment.

- ***Gastrointestinal clinical symptoms:***

Abdominal pain, episodic nausea and throwing up, abdominal bloating, and rotating constipation and diarrhea have been reported in the paediatric Fabry population. These signs might be related to intestinal dysmotility due to free dysfunction. Intestinal signs of modified bowel actions and abdominal pain have actually been reported in approximately 60% of children less than 10 years of age [24].

- **Complications in other aspects:**

- **Impact of FD in Quality of life of patients:**

An evaluation conducted in Mainz showed that organ participation in female patients with Fabry disease has a significant effect on QoL. Before initiating ERT, 15 female patients were asked to finish the short form 36 (SF-36) QoL questionnaire. The outcomes were compared with those from a general German population and from patients with different persistent diseases. Female patients with Fabry disease had SF-36 ratings that were substantially lower than those for the basic female population. Female patients with Fabry disease likewise scored significantly lower than females with rheumatoid arthritis in 'basic health', 'vitality', 'function emotional' and 'mental health' domains [25]. patients with FD clearly have lower QoL ratings in comparison with the healthy population. In the analysis of these results, some of the research study attributes need to be taken into consideration; firstly, disease intensity is hardly ever comprehensively reported and if reported, the data differs between studies. When measuring QoL ratings [26], Rombach et al. revealed that disease intensity plays an important function for determining QoL and ought to therefore be taken into account. In addition, more serious kidney disease has actually been revealed to result in decreased QoL, in particular after initiation of renal replacement treatment [27]. Baumstarck et al. showed that generic surveys typically are better for universal applications where QoL is compared in various populations, while disease particular instruments concentrate on particular health issue and are more delicate for identifying and quantifying small changes [28,29]. This would suggest that a Fabry specific QoL questionnaire would supply a more sensitive tool to investigate the results of enzyme replacement treatment on the QoL. At this point no validated FD specific QoL survey exists and it would be worthwhile to establish such a survey for this patient group. In spite of being large, these computer system registries have their imperfections as has been released by Hollak et al. [30]. Follow-up data on QoL of just a very small portion of patients enrolled in these windows registries were readily available for the analysis making the outcomes vulnerable to choose bias.

- ***Cerebrovascular complications:***

Cerebrovascular complications of stroke and transient ischaemic attacks have actually been documented in 5 - 27% of heterozygous women [7,31,32], with one study finding them more frequently in female than in male patients (27% compared to 12%) [32]. Mitsias and Levine reported 10 heterozygotes with cerebrovascular problems, such as amnesia, lightheadedness, ataxia, hemiparesis, loss of awareness and hemisensory disturbance [33]. Corresponding changes on magnetic resonance imaging (MRI), consisting of scattered white matter disease and infarction of the brainstem and thalamus, have been explained [34,35]; however, Morgan et al. cannot find any modifications on brain MRI in more youthful females [36]. Other neurovascular manifestations, consisting of vertigo, ringing in the ears, hearing loss and hypohidrosis, are reported in approximately one-third of female patients, and Galanos et al. suggested that the existence of anhidrosis in females is predictive of later significant renal disease [31].

- ***Renal complications:***

Renal failure is a substantial reason for premature death in male hemizygous patients with Fabry disease. On the other hand, whilst proteinuria [37] and a decrease in renal function are well explained in heterozygotes [38], progression to end-stage renal failure is infrequent, with just 1-- 2% of women requiring dialysis or hair transplant [7,32]. Histological evidence of kidney modifications has actually been discovered not only in those females with proof of renal dysfunction but likewise in asymptomatic heterozygotes going through examinations as potential kidney donors [39]. Due to the fact that of fever of unknown origin and renal failure [40], Kriegsmann and colleagues published a case report of a 26-year-old female patient who was confessed to hospital. Extracapillary proliferative (crescentic) glomerulonephritis and granulomatous interstitial nephritis were determined by histological, immunohistochemical and electron tiny analysis of a kidney biopsy, and Fabry disease was validated by more investigations [41].

4. CONCLUSION

Fabry disease is uncommon and provides with varied symptoms in childhood and medical diagnosis is frequently delayed. Physicians needs to be familiar with early signs and symptoms of Fabry disease, which should be thought about in the differential diagnosis when a young patient presents with several non-specific or unusual but reoccurring or episodic signs, particularly inexplicable neuropathic pain, gastrointestinal signs, workout tiredness, intolerance and hypohidrosis.

REFERENCES

[1] Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54. doi: 10.1001/jama.281.3.249.

[2] Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S, et al. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet. 1999;105:151–6. doi: 10.1007/s004399900075.

[3] Gold KF, Pastores GM, Botteman MF, Yeh JM, Sweeney S, Aliski W, et al. Quality of life of patients with Fabry disease. Qual Life Res. 2002;11:317–27. doi: 10.1023/A:1015511908710.

[4] Mechtler TP, Stary S, Metz TF, De Jesus VR, Greber-Platzer S, Pollak A, et al. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. Lancet. 2012;379:335–41. doi: 10.1016/S0140-6736(11)61266-X.

[5] Spada M, Pagliardini S, Yasuda M, Tukel T, Thiagarajan G, Sakuraba H, et al. High incidence of later-onset fabry disease revealed by newborn screening. Am J Hum Genet. 2006;79:31–40. doi: 10.1086/504601.

[6] van der Tol L, Smid BE, Poorthuis BJ, Biegstraaten M, Deprez RH, Linthorst GE, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet. 2014;51:1–9. doi: 10.1136/jmedgenet-2013-101857.

[7] 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. doi: 10.1136/jmg.38.11.769.

[8] Gupta S, Ries M, Kotsopoulos S, Schiffmann R. The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease a cross-sectional study of a large cohort of clinically affected heterozygous women. Medicine. 2005;84:261–8. doi: 10.1097/01.md.0000178976.62537.6b.

[9] Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab. 2008;93:112–28. doi: 10.1016/j.ymgme.2007.09.013.

[10] Meehan SM, Junsanto T, Rydel JJ, Desnick RJ. Fabry disease: renal involvement limited to podocyte pathology and proteinuria in a septuagenarian cardiac variant. Pathologic and therapeutic implications. Am J Kidney Diseases Off J National Kidney Foundation. 2004;43:164–71. doi: 10.1053/j.ajkd.2003.09.022.

[11] Desnick RJ, Ionnou Y, Eng CM. Fabry disease: alpha galac- tosidase A deficiency. In: Scriver CH, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. New York: McGraw Hill, 1995:2741-84.

[12] Ropers HH, Wienker TF, Grimm T, Schroetter K, Bender K. Evidence for preferential X-chromosome inactivation in a family with Fabry disease. *Am J Hum Genet* 1977;29:361- 70.

[13] Desnick RJ, Raman MK, Bendel RP, et al. Prenatal diagnosis of glycosphingolipidoses: Sandhoff's and Fabry's disease. J Pediatr 1973;83:149-50.

[14] Vedder AC, Strijland A., vd Bergh Weerman MA, et al. Manifestations of Fabry disease in placental tissue. J Inherit Metab Dis 2006;29:106-11.

[15] Tsutsumi A, Uchida Y, Kanai T, et al. Corneal findings in a fetus with Fabry's disease. Acta Ophthalmol (Copenh) 1984;62:923-31.

[16] Hopkin RJ, Bissler J, Banikazemi M, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry registry. Pediatr Res 2008;64:550-5.

[17] Laney DA, Peck DS, Atherton AM, et al. Fabry disease in infancy and early childhood: a systematic literature review. Genet Med 2015;17:323-30.

[18] Alfadhel M, Sirrs S. Enzyme replacement therapy for Fabry disease: some answers but more questions. Ther Clin Risk Manag 2011;7:69-82.

[19] Burlina AP, Sims KB, Politei JM, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. BMC Neurol 2011;11:61.

[20] Kolodny EH, Pastores GM.. Anderson-Fabry disease: extrarenal, neurologic manifestations. J Am Soc Nephrol 2002;13 Suppl 2:S150-3.

[21] Cabrera-Salazar MA, O'Rourke E, Charria-Ortiz G, et al. Radiological evidence of early cerebral microvascular disease in young children with Fabry disease. J Pediatr 2005;147:102-5.

[22] Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. QJM 2010;103:641-59.

[23] 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.

[24] 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.

[25] Bähner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. J Inherit Metab Dis. 2003;26:617–27.

[26] Rombach SM, Hollak CE, Linthorst GE, Dijkgraaf MG. Cost-effectiveness of enzyme replacement therapy for Fabry disease. Orphanet J Rare Dis. 2013;8:29. doi: 10.1186/1750-1172-8-29.

[27] Wagner M, Kramer J, Blohm E, Vergho D, Weidemann F, Breunig F, et al. Kidney function as an underestimated factor for reduced health related quality of life in patients with Fabry disease. BMC Nephrol. 2014;15:188. doi: 10.1186/1471-2369-15-188.

[28] Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P. Measuring the quality of life in patients with multiple sclerosis in clinical practice: a necessary challenge. Multiple Sclerosis Int. 2013;2013:524894. doi: 10.1155/2013/524894.

[29] Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989;27:S217–32. doi: 10.1097/00005650-198903001-00018.

[30] Hollak CE, Aerts JM, Ayme S, Manuel J. Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders. Orphanet J Rare Diseases. 2011;6:16. doi: 10.1186/1750-1172-6-16.

[31] Galanos J, Nicholls K, Grigg L, Kiers L, Crawford A, Becker G. Clinical features of Fabry's disease in Australian patients. Intern Med J. 2002;32:575–84.

[32] Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C. et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004;34:236–42.

[33] Mitsias P, Levine SR. Cerebrovascular complications of Fabry's disease. Ann Neurol. 1996;40:8–17.

[34] Grewal RP, McLatchey SK. Cerebrovascular manifestations in a female carrier of Fabry's disease. Acta Neurol Belg. 1992;92:36–40.

[35] Hasholt L, Sorensen SA, Wandall A, Andersen EB, Arlien-Soborg P. A Fabry's disease heterozygote with a new mutation: biochemical, ultrastructural, and clinical investigations. J Med Genet. 1990;27:303–6.

[36] Morgan SH, Rudge P, Smith SJ, Bronstein AM, Kendall BE, Holly E. et al. The neurological complications of Anderson–Fabry disease (α-galactosidase A deficiency) – investigation of symptomatic and presymptomatic patients. Q J Med. 1990;75:491–507.

[37] Yuen NW, Lam CW, Chow TC, Chiu MC. A characteristic dissection microscopy appearance of a renal biopsy of a Fabry heterozygote. Nephron. 1997;77:354–6.

[38] Rodriguez FH Jr,, Hoffmann EO, Ordinario AT Jr,, Baliga M. Fabry's disease in a heterozygous woman. Arch Pathol Lab Med. 1985;109:89–91.

[39] Gubler MC, Lenoir G, Grunfeld JP, Ulmann A, Droz D, Habib R. Early renal changes in hemizygous and heterozygous patients with Fabry's disease. Kidney Int. 1978;13:223–35.

[40] Kriegsmann J, Otto M, Wandel E, Schwarting A, Faust J, Hansen T. et al. [Fabry's disease, glomerulonephritis with crescentic and granulomatous interstitial nephritis. Case of one family] Pathologe. 2003;24:439–43.

[41] Kriegsmann J, Otto M, Wandel E, Schwarting A, Faust J, Hansen T. et al. [Fabry's disease, glomerulonephritis with crescentic and granulomatous interstitial nephritis. Case of one family] Pathologe. 2003;24:439–43.