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Clinical Features and Complications of Fabry Disease

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Abstract: **Fabry disease is an uncommon, X-linked shortage of α-galactosidase A, affecting approximately 2 - 5 people per 1 million live births. This study as comprehensive review aiming to discuss and overview the clinical symptoms and features of Fabry disease, as well as to emphasizes the complications associated with this familial disease. The Embase, PUBMED/MEDLINE databases were searched for articles published until December 30, 2016. We included in this review every types of studies (reviews, randomized control trails, and systematic reviews) except case reports. The search strategies were through PUBMED/MEDLINE used following Mesh terms to identified relevant studies easily: (fabry disease OR fabry's disease) AND (Complications, & clinical features. Only Human studies of reviews, meta-analysis, randomized controlled trials published in English language were included. complications of Fabry disease, such as stroke and kidney and cardiac arrest, and poor quality of life, have been revealed by numerous proof based studies, though these complications are not typical among children. The manifestations of this complex disease are multisystemic and progressive. The classic kind is seen in both males and women, although the manifestations are typically less serious in females and disease development is usually postponed compared with males.**

Keywords: **Fabry disease, clinical symptoms, meta-analysis, Human studies, clinical features.**

1. INTRODUCTION

Fabry disease is an uncommon, X-linked shortage of α-galactosidase A, affecting approximately 2 - 5 people per 1 million live births. Common presenting symptoms include acroparaesthesiae, hypohidrosis, cutaneous angiokeratomas and cornea verticillata. In hemizygous males, the condition manifests nearly widely, while a percentage of heterozygous females are also impacted [(1,2)]. Scientific symptoms normally become apparent in youth, and the medical diagnosis is often suspected on the basis of a positive family history. Around 60% of patients with manifest Fabry disease report gastrointestinal signs [(3)]. This compares to a prevalence of 77% for neuropathic pain, 78% for sensorineural deafness, 30% for renal failure and 24% for cerebrovascular disease. Not generally life threatening, intestinal signs can have a major unfavorable effect on quality of life [(2,4,5,6)]. Early signs in classically impacted male and female patients consist of angiokeratoma, anhydrosis, neuropathic pain, gastrointestinal signs and microalbuminuria. Later in life, progressive renal failure, cardiac arrest and stroke typically take place. In non-classically impacted male patients and a lot of women, the disease presents with a more attenuated and variable disease course [(7,8)]. The shortened life span and the morbidity of Fabry patients are strongly related to the degree of end-organ damage [(8)].

Patients who suffer from FD have a lower quality of life (QoL) compared to healthy individuals. Neuropathic pain and anhidrosis are predictors of reduced QoL, presumably as a marker of more extreme disease [(9)]. It has been postulated that ERT has a positive result on QoL [(10,11)]. These research studies used different procedures of QoL and were only reported for small mates of patients. Interest in QoL measurements has increased over the past decades, because it is well recognized that, in addition to handicaps, psychological and psychological factors play an important function in the lives of patients with FD. Additionally, patient involvement with decision making and assessment of quality of care is

increasing. QoL measurements are needed for cost-effectiveness analyses, nowadays a requirement for reimbursement of therapy for some governments in the EU [12].

This study as comprehensive review aiming to discuss and overview the clinical symptoms and features of Fabry disease, as well as to emphasizes the complications associated with this familial disease

2. METHODOLOGY

The Embase, PUBMED/MEDLINE databases were searched for articles published until December 30, 2016. We included in this review every types of studies (reviews, randomized control trails, and systematic reviews) except case reports. The search strategies were through PUBMED/MEDLINE used following Mesh terms to identified relevant studies easily: (fabry disease OR fabry's disease) AND (Complications, & clinical features. Only Human studies of reviews, meta-analysis, randomized controlled trials published in English language were included.

3. RESULTS

- ***Pathophysiology of fabry disease:***

Deficiency of α-galactosidase A results in progressive intracellular accumulation of the cell membrane-derived glycolipid, globotriaosylceramide (Gb3). Gb3 accumulates within the cytoplasm and lysosomes of affected cells, and might be spotted microscopically as a foamy deposit within the cell or ultrastructurally as electron-dense intralysosomal striped 'zebra-like' 0.5-- 0.75 μm bodies [4]. Gb3 accumulates most plainly in endothelial, perineural and perithelial cells, cardiomyocytes, kidney glomerular cells, and neurones. Small unmyelinated neurones, such as those responsible for peripheral pain perception and those in the enteric nervous system, are most impacted [13,14].

The lack of α-galactosidase A, which catalyses the breakdown of specific glycosylceramides, might also impact the accumulation of other lipids, such as isoglobotriaosylceramide (iGb3), which was just recently determined as an endogenous ligand for the CD1d particle [15]. CD1d is homologous to major histocompatability complex class I molecules and is considered vital for the function of natural killer T lymphocytes (NKT cells), which bear a limited subset of invariant T cell receptor molecules and acknowledge glycolipid antigens [16]. Up until just recently, the likely endogenous or exogenous ligand for NKT cells and CD1d had actually not been recognized, and an artificial form of a marine sponge-derived glycolipid, α-galactosylceramide, was the most widely utilized speculative ligand. Recent research, however, has recognized endogenous iGb3 and glycolipids derived from the cell walls of Gram-negative germs as the most likely physiological and pathophysiological ligands [15,17]. The CD1d-dependent pathway of NKT cell activation is thought about highly crucial in the upkeep of host defence in the intestine, and it is possible that some aspects of gastrointestinal symptomatology in Fabry disease may connect to yet unidentified and subtle immunological modifications [18].

- ***Clinical features of Fabry disease:***

Gastrointestinal symptoms:

The most commonly reported gastrointestinal sign in afflicted patients is diarrhoea, with frequent loose bowel movements and cramping abdominal pain. Patients typically complain of postprandial signs, including urgency, diarrhoea and flatulence. Stool frequency in patients with Fabry disease can be as high as 10 - 12 soft or semi-solid motions per day; however, in contrast to inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, patients do not typically report rectal passage of mucous or blood. In lots of patients, episodes of diarrhoea are interspersed with durations of normal, and even lowered, bowel activity, when they might suffer constipation; this alternating pattern is reminiscent of irritable bowel syndrome (IBS) [19].

Patients may likewise experience a sense of early satiety after meals, epigastric pain and stomach bloating. These signs may lead them to avoid meals and to report a decreased appetite. Once again, the signs of stomach discomfort and bloating associated with meals are features of IBS. Altered gastric emptying, which is ameliorated by treatment with metoclopramide, has likewise been reported in Fabry disease [20]. Sharp or stabbing epigastric pain, dyspepsia and heartburn suggest alternative diagnoses, such as peptic ulcer disease or gastrooesophageal reflux, and ought to prompt proper examination and treatment. The CD1d-dependent path of NKT cell activation is thought about highly essential in the maintenance of host defence in the intestine, and it is possible that some elements of gastrointestinal symptomatology in Fabry disease might relate to as yet unknown and subtle immunological modifications [18]. From the preceding

discussion, it is apparent that almost all the cells and systems that add to intestinal structure and function may be affected by Fabry disease; the various targets are illustrated in (**Figure 1**) [18].

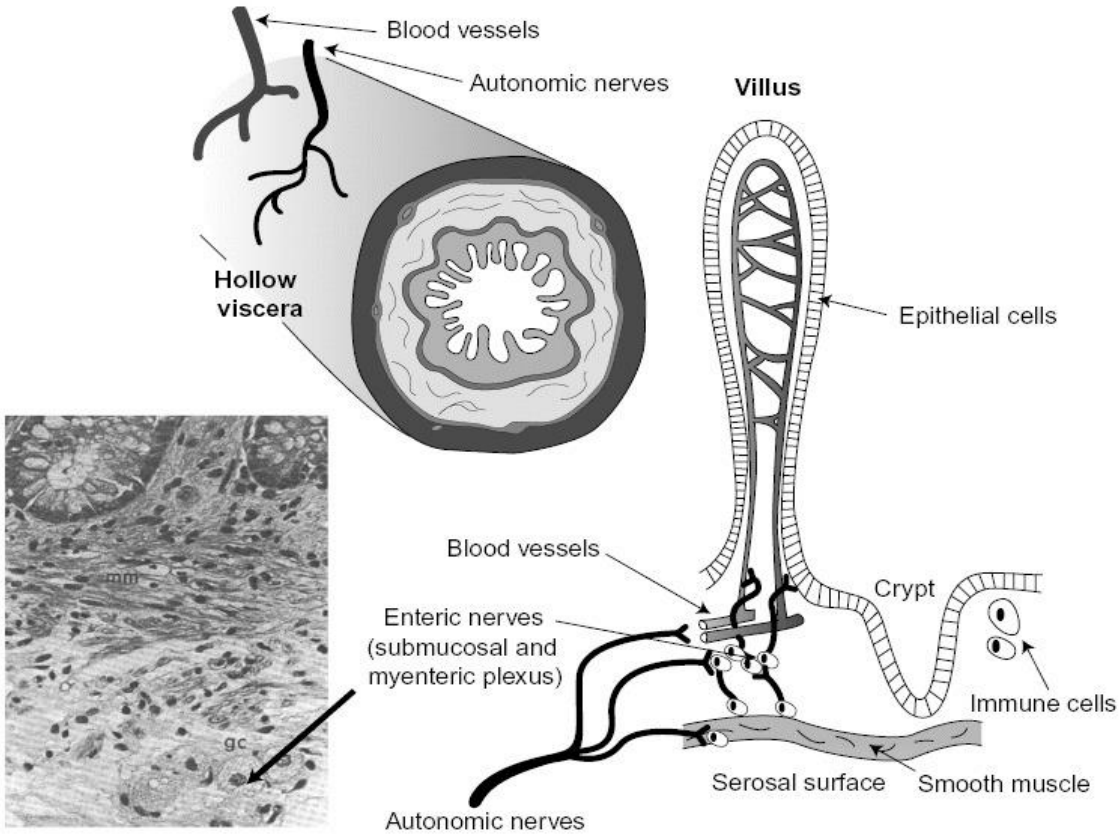

Figure1: Main features of the hollow gastrointestinal viscera that may be affected by Fabry disease [4]

In addition, diarrhoea and abdominal pain are two essential symptoms in intestinal practice that frequently, when they are not caused by recognizable natural pathology, show a kind of IBS. This syndrome has a total population frequency of up to 15% in some neighborhoods [19]. The striking resemblance in medical findings in between a typical case of Fabry-related gastrointestinal disease is summarized in (**Table 1**) [19].

Table 1: Clinical features of the gastrointestinal manifestations of Fabry disease. [19]

Fabry disease
Diarrhoea
Abdominal pain
Postprandial exacerbation of gastrointestinal symptoms
No rectal bleeding
Normal 'routine' blood tests in early stages (i.e. blood count, urea and electrolytes, erythrocyte sedimentation, C-reactive protein)
Normal upper endoscopy and colonoscopy (usually)
Symptoms associated with autonomic and enteric neuropathy

Renal Symptoms and complications in Fabry disease:

Kidney involvement prevails in traditional Fabry disease and is an essential cause of death. Irregularities consist of proteinuria, haematuria, nephrotic syndrome and persistent kidney failure requiring dialysis and/or kidney hair transplant [21,22]. Proteinuria might be apparent throughout childhood. Data from FOS show that proteinuria happens in 10% of boys and 17% of girls with Fabry disease. Onset of end-stage renal failure normally takes place in male patients when they

remain in their 30s and is not seen in childhood. Irregularities of kidney function are regularly seen in females; however end-stage kidney failure is unusual [22].

Cardiovascular features:

Heart disease is among the most regular causes of death in patients with Fabry disease. Typical heart defects include left and right ventricular hypertrophy, bigger left atrium, heart valve irregularities and conduction disturbances. Heart participation might be the only sign in some hemizygous males [6], and as much as 5% of males with hypertrophic cardiomyopathy may have a 'cardiac' variant of Fabry disease [23].

CNS symptoms in Fabry disease:

Cerebrovascular symptoms such as transient ischaemic attacks or stroke have been reported to affect 15-- 20% of patients with Fabry disease, and such attacks frequently recur and indicate a poor prognosis [24,25]. Data from big study show that some 6-- 9% of patients have experienced stroke; however, this value may be an underestimate of the true frequency due to the high number of patients in the early stages of the disease who are included in this database. A current research study has actually indicated a frequency of Fabry disease as high as 5% in males and 2.5% in females under the age of 55 years presenting with 'cryptogenic' stroke-- that is, stroke happening in the absence of other obvious risk factors (26). Disrupted concentration, dizziness, dementia, headaches and finding out problems also take place [2].

Respiratory complications and symptoms in Fabry disease:

Substantial airflow obstruction prevails in patients with Fabry disease. Hence, smoking cigarettes is particularly inadvisable as it seriously worsens lung problems [27]. Shortness of breath, tiredness and tiredness prevail symptoms in early adulthood, and these symptoms develop as a result of cardiac, renal and pulmonary deficiency. Asthma and reversible airways blockage also occur [27]. Most of the literature describes symptoms and indications of pulmonary participation such as dyspnoea, wheezing, and dry cough in Fabry disease [28,29]. Also intermittent chest tightness, pneumothorax [30,31], haemoptysis [31], recurrent pulmonary infections [31], pulmonary thromboembolism [31], pulmonary infarction [30,31] and shortness of breath and acral cyanosis upon minimal exertion [6,7].

4. CONCLUSION

Life-threatening complications of Fabry disease, such as stroke and kidney and cardiac arrest, and poor quality of life, have been revealed by numerous proof based studies, though these complications are not typical among children. The manifestations of this complex disease are multisystemic and progressive. The classic kind is seen in both males and women, although the manifestations are typically less serious in females and disease development is usually postponed compared with males.

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