CLINICAL SYMPTOMS, EFFECTIVE CURE AND HAZARDOUS EFFECTS OF FABRY DISEASE ON HUMAN HEALTH

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Abstract

Fabry disease is a lysosomal storage disorder which is caused by the deposition of globotriaosylceramide (GL-3) due to the deficiency of a-galactosidase A leading to the change in metabolism. This is a pan ethnic disorder and more frequently present in males than in females. Children may also have the symptoms of this disease. The major symptoms of fabry's disease are pain in body, anaemia, fever, kidney problems, dermatological symptoms and cardiovascular disease and strokes. The disease can be analysed by the DNA testing in amniotic cells and chorionic villi and enzyme activity. Atypical variants or available genetic therapy may complicate the genetic counselling. The disease specific treatment has been introduced in which recombinant human galactosidase enzyme is used to investigate the fabry's disease, this treatment is known as enzyme replacement therapy. Renal transplantation and dialysis have also been introduced. Analgesic drugs, antiarrhythmic agents and nephroprotections are used to relieve pain.

Keywords: galctosidase, lysosomal, X-linked, pan ethnic, enzyme replacement therapy.

1.0 **Introduction**

Fabry disease is X-linked, progressive inborn metabolic disorder (Anderson, 1898). Fabry disease (FD) can also be known as Fabry's disease, α-galactosidase - A deficiency and Anderson Fabry disease. Fabry disease is second commonest lysosomal storage disorder which arises because of the shortage of an enzyme GAL-A (ceramide trihexosidase) activity, this enzymes is involved in the catabolism of glycosphingolipid. globotriaosylceramide (GL-3) starts to deposit in all over the body, especially in the vascular endothelium. Anderson's fabry disease most commonly affects the males, but the heterozygous carrier females can also be faced this disease because of the random or accidental inactivation of X-chromosome. The expected occurance of FD is 1 of the 40,000 - 60,000 males (Desnick *et al.*, 2001). Fabry disease (FD) was firstly recognized about hundred years ago, but no specific treatment for this disease has been available till now. The symptoms of fabry disease i.e; angiokeratomas gastrointestinal, burning sensations, pain in hands and feet and temperature intolerance can be seen earlier in the childhood. These signs can lead to the premature death or end-organ failure. These are glomerulosclerosis and proteinuria, arrhythmia and cardiac hypertrophy, some strokes and cardiovascular disease (Zarate and Hopkin, 2008; Germain, 2010). Now-a-days, patients are going to be managed with nonspecific and supportive treatment for cerebrovascular and cardiac complications, pain management and end-stage kidney problems. Enzyme replacement therapy (ERT) for this fabry's disease has been used recently to stabilize kidney functions and to reduce pain in patients (Schiffmann, *et al.*, 2001).

Sphingosine-Glucose-Galactose-Galactose + H2O ---→ Sphingosine-Glucose-Galactose + Galactose

2.0 **Signs and symptoms**

Early neural damages i.e; nerve fibres of autonomic and somatic nervous system occur primarily at an early age in girls and boys (Hopkin *et al.*,2008). Pain is the earliest symptom

of this disorder that is being experienced by 60 to 80% of affected patients. This pain can be of two types: episodic crises describe as the burning pain which produce in the fringes and then moves inwards to the limbs and then towards the other parts of body, second one is the chronic pain which is characterized by tingling and burning paraesthesias (Charrow, 2009). Episodic crises might be activated by fever, quick temperature changes, fatigue, exercise, and stress (Hilz *et al.*, 2000). Patients with this disease have a reduced life quality (Miners *et al.*, 2002). In newly affected adult patient, it is very important to analyse the medical history of the patient's childhood either he had acroparathesia or not. Gastrointestinal involvement is an under- appreciated but common sign of Fabry's disease. These symptoms might be occurring due to extra accumulation of Gb3 in the mesenteric blood vessels and in the bowel. Anhidrosis (absence of sweating) or hypohidrosis (decreased rate of sweating) is also an important problem for patients of this disorder and cause exercise and heat intolerance (Germain, 2002; Eng *et al.*, 2006). Angiokeratoma (skin lesions) is another most visible medical feature of this disorder, the small red colored clusters of raised skin cuts are normally found on the groin, upper thighs and navel and the mucosal parts of mouth. The main causes of these lesions are the collective damage in the cells of vascular endothelial; these cells may rise in size and number with age and can be produce in groups or singly (Germain, 2002). Cornea verticillata (Corneal changes) as shown in fig.1, are hardly of visual importance and can be detectable easily.

Fig. 1: Cornea verticillate

In children, the tinnitus and the loss of hearing have also been (Keilmann *et al.*, 2009). During adolescence gaining of weight becomes difficult and Chronic fatigue can also been observed. Fifty patients of this disease are reported to have proteinuria which is the most important renal symptom; this shows the renal involvement in fabry disease as shown in fig.2. Mild albuminuria is the first indication of renal disease in children and adults during adolescence. Before the progression of proteinuria vascular and glomerular changes occur, this result has been shown by biopsy studies. So, renal biopsy plays an important in the detection of kidney problems.

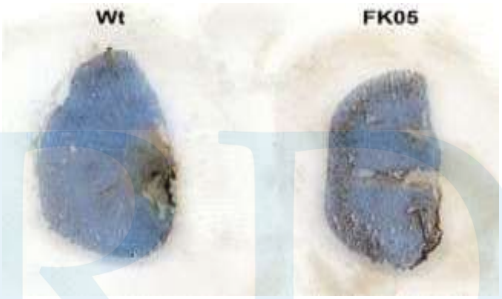

Fig. 2: Renal involvement in fabry disease

All of the cardiac structures, i.e; conduction system, valves and the myocardium can also be affected in patients of this disease (Frustaci *et al.*, 2007). Angina pectoris has also been reported in patients of this disease. Arrythmia is also the commonest symptom of this disorder in patients and as the age increases, the rate of arrythmia increases in both genders.

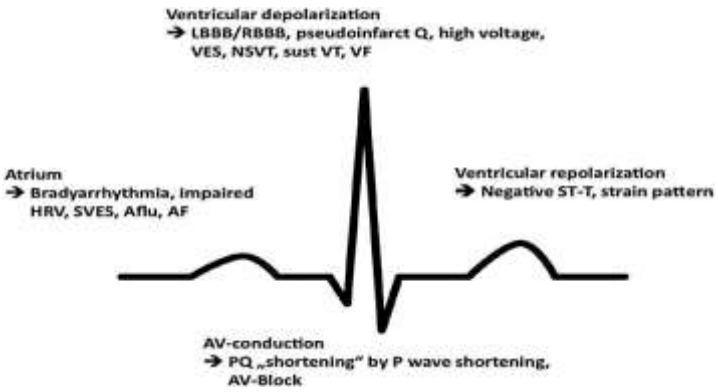

Fig. 3: Electrocardiogram

Intermittent ventricular tachycardia and paroxysmal atrial fibrillation are also the common cardiac symptom of FD. LVH has also been identified in 50 % patients but more common in males than females. It is closely associated with the occurance of valvular disease, cardiac signs such as thickness of carotid artery and arrhythmia (Barbey *et al.,* 2006). Stroke and Transient ischaemic attack (TIA) are been often observed in patients of this Fabry disease (Mehta *et al.,* 2004; Buechner *et al.*,2008). Renal and cardiac problems due to fabry disease are associated with cerebrovascular disease. Angiokeratomas is a Dermatological sign (fig.4) of this disease but not specific for this disease. 66% and 36% of total males and females respectively are facing this disease. Diffused angiokeratomas are generally located on lower trunk. Some other important symptoms are lymphoedema, hypohidrosis and talengiectasia but these symptoms are more common in males (Orteu *et al.*, 2007).

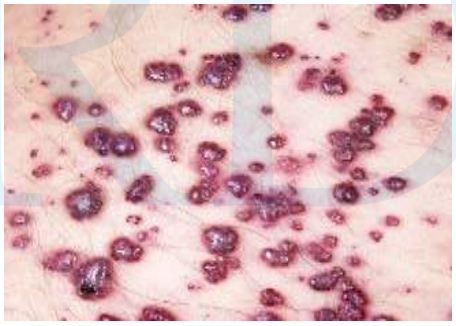

Fig. 4: Dermatological signs

The most commonly reported symptoms are neurological symptoms which occur in 80% of fabry's patients (Mehta *et al.,* 2004). Neuropathic pain is being observed in both males and females (Hoffmann *et al.*, 2007). Pain is frequently felt in hands or in feet. Patients with fabry disease got serious Depression problems. Patients having this symptom should avoid smoking. Fever and anemia are also reported as the frequent symptoms of fabry disease. All these symptoms may have serious effect on the patient's life quality. ERT has been introduced to overcome this disease.

3.0 **Pediatric fabry disease**

The common signs are generally arise during childhood or in puberty stage. A report was prepared by Pintos Morell and Beck about the fabry disease in children which concludes that the neuropathic pain, gastrointestinal problems and hypohidrosis are the most commonly observed symptoms of fabry's disease in children. The young patients may also face the problems of kidney dysfunction, LVH and stroke. Ries and Shis collegues studied the agalsidase alfa in children; they treated 5 girls and 19 boys for six months. Then they reported that Agalsidase alfa was usually well tolerated, patients who take the anticonvulsant medication at baseline able to withdraw the medications. Quantitative sudomotor axon reflex testing was also done to check the sweat functions in 13 patients and been observed the rise in volume of sweat from 0.48 L/mm2 to 0.73L/mm2 in six months (Ries *et al.*, 2006).

4.0 **Women with fabry disease**

It was considered that fabry disease affects only to the males, but later it was observed that heterozygotic females also have the symptoms of this disease. Women normally develop the phenotypic expression of the disorder ten years later than in females and these expressions are more severe and have more progression rate (Wilcox *et al.*, 2008). A study to check the effects of ERT in affected females with this disrease has also been reported. Whybra and his collegues (Whybra *et al.*, 2009) had treated thirty-six females who have adopted these symptoms with agalsidase alfa atleast for four years. No studies have exactly been designed to inspect the special agalsidase β effects in women.

5.0 **Enzymatic and molecular diagnosis**

4-methylumbelliferyl-D-galactoside is basically used as a substrate to analyse the lack of galactosidase A activity in leukocytes, more reliably in men than in women. Some show

normal activity of Gal-A, therefore, its assay is not useful for carrier detection. Molecular studies should have to be done to check the risk of this disease in females by identifying the mutations in their family history. To diagnose the fabry disease, genetic counceling is important to provide the basic information about the disease and its treatment such as ERT to the patients. This disease can also be analysed prenatally by studied the deficient activity of Gal- A in amniocytes and XY karyotype (Brady *et al.*, 1971). Molecular studies may replace the enzymatic diagnosis, if the mutation in Gal-A occur.

5.1 Screening

In heterozygous females, Gal A activity is frequently occurs in the normal range. A complete analysis of this disease offers the opportunity to stabilized function of different organs by replacing the deficient enzyme. Screening of patients having idiopathic renal, cerebrovascular and cardiovascular problem can also detect FD that can be benefitted by ERT. This disease can also be described in females, in end-stage renal problem and it can be checked by haemodialysis screening (Terryn *et al.*, 2008).

In females, screening of hypertrophic cardiomyopathy can also identify the occurance 1% of fabry disease of 1% (Monserrat *et al.*, 2007). According to a survey in Northern Italy from 2003 – 2005, newborn screening programme shows much higher occurance of this disease as compared to previously suspected.

6.0 **Disease pathophysiology**

Human body contains Glycosphingolipids which are usually present in the plasma membrane of different cells. RBC's are known to be as important contributor to study the pathophysiology. The principal glycosphingolipid is frequently known as globoside when it is present in erythrocyte stroma and can also be called as globotetraosylcermide. On the level of

senescent these cells are removed by tissue macrophages from blood circulatory system. The membrane components of phagocytized cells start to degrade with the help of enzymes into subcellular sorganelles known as lysosomes. This catabolism of the globoside starts with the help of an enzyme 'hexosaminidase-B' that forms the globotriaosylceramide (Gb3). The pathological quantity of globotriaosylceramide (Gb3) starts to accumulate in the body of patient of this disease due to the deficiency α-galactosidase A. This accumulation of globotriaosylceramide take place in organs and tissues of rats when this enzyme is eliminated (Ohshima *et al.,* 1997) but mice showed no symptoms of this disease. Therefore, they resembls to the p blood group of human that also do not have Gb4 or Gb3 in RBC's because of the complete absence of an enzyme Gb3 synthase, this enzyme has catalytic activity and is important in the breakdown of of galactose to ceramidelactoside (Furukawa *et al.,* 2000).

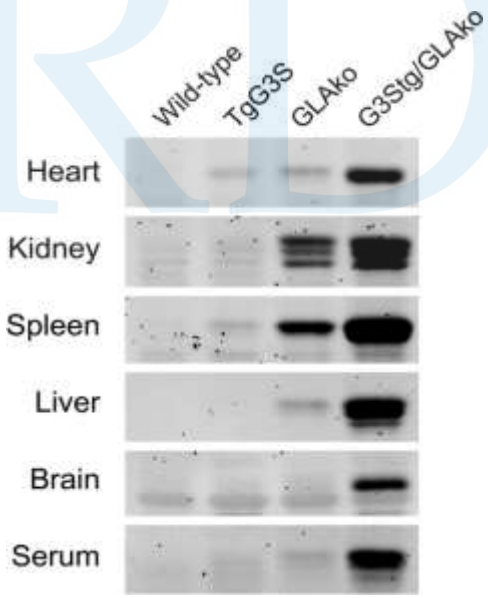

Fig. 5: Fabry's disease in rat

7.0 **Atypical variants of Fabry disease**

In males those affected with classic or variant phenotype, disease could be diagnosed by regulating the activity of α-Gal A in the peripheral or plasma leukocytes. Atypical male

variant has a milder, later onset phenotype (Desnick *et al.*, 2001). These patients donot have early clinical manifestations of fabry disease because of low residual levels of α-Gal A. For example people some cardiac variants who are present with mild proteiniuria and cardiomegaly after fouty years of age when patients with the 'classic Fabry diease' would have been severely affect or dead. For Females, they have normal to low activity of α-Gal A so there family mutation, specific, must be known. Mutations for greater than 300, have been figured out, the most of which are nonsense, amino acid substitution, or missense, which causes the premature truncation in the amino acid sequences and other deletions, insertions, and splicing effects have also been noted. However, De novo mutations have found to be rare.

8.0 **Therapies**

8.1 Enzyme replacement therapy

ERT is the Supportive therapy for Fabry Disease. It includes pain control with the painkillers, non-steroidal anti-inflammatory agents, anticonvulsants, including treatments of cardiac, renal comorbidities with antiplatelet and antihypertensive agents, cerebrovascular, dialysis and, the end stage renal disease known as kidney transplantation. Particular treatment which consists of the enzyme replacement therapy (ERT) with the recombinant αGAL-A. Agalsidase alfa has been manufactured by the Shire Human Genetic Therapies from the cell lines of human and then overseen regularly two weeks by the intravenous infusion at the dose of the 0.2 mg/kg. Agalsidase beta has been manufactured by the Genzyme Corporation which had been recently acquired via Sanofi-Aventis, from the Chinese hamster ovary cells and overseen with the intervals of two weeks through intravenous infusion at the dose of 1.

8.2 Molecular Chaperone Therapy

A discovery, that has been made, that certain tiny inhibitor molecules of α-galactosidase A

has the capacity to rise the catalytic bustle of few of mutated forms of the respective enzyme. This has encouraged to the investigation and identification of these agents that can be useful, therapeutically. Now this particular approach leans to remain rational for a huge portion (~45%) of the nonesense mutations α-galactosidase. A gene in the patients having the Fabry disease don't result in noticeable residual enzyme (Desnick *et al.*, 2001). This situation impedes numerous patients with the Fabry disease to take benefit from this therapy. However, to identify the patients who could be benefitted through chaperon therapy, a well-organized process was established to evaluate the grade to which α-galactosidase A could enhance its catalytic bustle through molecular chaperon. The application of this technique should provide assistance that who could be benefitted by this therapy.

8.3 Substrate Reduction Therapy

Via blocking a certain enzymatic step during biosynthesis of the substance that accumulates, SRT is accomplished. This was thought to remain of interest in the Fabry disease to observe the influence of obstructing the accumulation of the glucose to the ceramide that will result in the reduced formation of Gb. Consequently, the effect of an inhibitor of the glucocerebroside biosynthesis got to be inspected in the 'Fabry mice'. A huge reduction of Gb3 (~ 50%) got to be observed in liver, heart and kidney ensuing eight weeks of the intra-peritoneal supervision of the inhibitor. The specific mechanism of the allowance of Gb3 from these organs of the mice which lacked α-galactosidase A is not been recognized yet. Nonetheless, advancing examination of substrate reduction therapy acts to be defensible in the patients suffering from Fabry disease.

8.4 Gene Therapy

The convenience of the α-galactosidase A/knock-out mice (Ohshima *et al.*,1997) made possible to start few serious experiments in the respect to plaid gene therapy for the patients

having Fabry disease. Related findings in the respective investigations included substantial drops of the collected Gb3 succeeding solo injection of 'a recombinant adeno-associated viral vector' which contained 'a modified chicken α-actin promoter'. At the 6th-month after supervision of that vector the raised Gb3 in spleen and liver was at normal level. There had a 66% reduction in lung and an 85% reduction in heart. Kidneys showed a reduction of 82% at 2nd month. However, at 6th month, the amount of the Gb3 in kidney returned to its 60% of the level that was before treatment. Due to the insertional mutagenesis which follows the use of retroviral vector causing leukaemia in human heirs, gene therapy for metabolic storagic disorders and for Fabry disease has been delayed). It is under consideration that by operating self deactivating lentival vectors which in the stem cell originated erythroid cells might reduce oncogenic problems that are correlated with the gene therapy, hence positive treatment for the patients having fabry disease shall be developed.

9.0 **Quality of life**

The objective of this literature review was to analyze the recent available data that concerned QoL, for this purpose questionnaires were used that patients who were suffering from FD equated in comparison to common population and the effects of ERT on QoL, 54 articles have been found to be relevant for this respective literature. Patients which had Fabry Disease had a lower quality of life in comparison to the common population. So, it was proposed that the particular questionnaire of Fabry disease should be prepare to perfectly assess the quality of life in effected patients of this disease.

On the study type, data got recorded (clinical trials, cohort studies, before-after studies, registry studies or case series), quantity of the gender, subject and their age sets (whether adults or children), with the questionnaire we have used to evaluate QoL. Meta-analysis had been made on the reports of SF 36 or RAND-36 results which used inverse variance-

weighting. Articles also contained in meta analysis when the 'mean realm' scored with the typical confidence or deviations interludes were being specified. 'Pooled analysis' aimed at all the reports joint, for subgroups studies as fine, were performed. Subcategories were being described as:

(1) Studies that were achieved in the phase earlier Enzyme Replacement Therapy was accessible (means unprocessed 'mostly characteristically affected victims').

(2) Reports on the consequence of Enzyme Replacement Therapy that reports boundary quantities (unprocessed patients. However, with an indication of cure).

(3) Studies which only included patients treated with ERT. Then results from the General health sub domains and Bodily Pain from the RAND-36 were omitted due to the use of altered scoring alogrithum. The search was electronic and it occasioned in 532 journals. By Double-checking the allusion list exposed 4 extra, pertinent, papers. After the elimination of the replications, 368 articles were still there. 187 articles got nominated from them grounded on their abstract and title. As a whole 54 articles got qualified for getting included in this respective review, of which only 26 reported QoL in detail.

9.1 Questionnaires prepared to evaluate QoL in patients with Fabry Disease

Fifteen different questionnaires were castoff to evaluate QoL in Fabry Diseased population, among which was the Brief Form Health Survey (SF-36), Europe's QoL, five measurements survey (EQ-5D) and intrusion mark of Brief Pain Inventory (BPI), had been the frequently utmost used actions. A short story of the surveys is described below. Extra surveys being castoff were: The Anderson-Fabry Disease, specific questionnaire, (Miners *et al.*, 2001, Child Health Questionnaire, FPHQP (Fabry-Specific Pediatric Health and Pain) Questionnaire

(Ramswami *et al.*,2012), KINDL (Ramswami *et al.*,2012), PedsQL (Wyatt *et al.*, 2012), RAND-36 and four locally developed questionnaires.

RAND-36 and SF-36

The SF-36 questionnaire evaluates eight spheres of Quality of Life:

(1) Role Physical, (2) Role functioning, (3) general health, (4) bodily pain, (5) Energy, (6) emotional role, (7) social functioning, (8) psychological health.

The domain of SF-36 grades the ranging '0 to 100'. These eight spheres were categorized in double summary scores; 'The Physical Component Summary (PCS)' and 'The Mental Component Summary' (MCS). RAND-36 is almost same as SF-36. But for the spheres, Bodily Pain and the General Health, the algorithms were dissimilar.

EQ-VAS and EQ-5D

The questionnaire, EQ-5D, included of five domains or shperes:

(1)Self care, (2) mobility, (3) usual activities, (4) depression, (5) discomfort (EuroQol-Group, 1990). Each of the domains has three stages of sternness:

There are no problems, (2) there are some or moderate problems, and (3) there are extreme problems. For calculating the score of QALYs (quality-adjusted life years) the results from EQ-5Dwas converted to a utility score via alogrithum that used population based preferences. Utility scores ranged from −0.1 to 1 or perfect health, and that zero meant negative or dead meant health situations even poorer than dead. An improvement or variance of 0.074 was pondered as clinically important. EuroQol Pictorial Analogue Scale (EQ-VAS), a pictorial analogue scale which varies as 0 to 100 and evaluates health condition. 7 is considered to be the minimal important difference.

9.2 BPI

Brief Pain Inventory was devised to evaluate the sternness of the pain and influence of the pain on its daily functions. The impact imitated by BPI interference score, that was mean of intrusion subscales: (1) mood, (2) general activity, (3) normal walk, (3) walking ability, (4) sleep, (5) relations to others and (6) enjoyment in life. The subscales were scaled as 0 to 10, having the assessed important alteration of 0.5 or 1 SD.

9.4 QoL in the patients having Fabry Disease against the common population

There were 11 studies made that examined Quality of Life in unit of Fabry Disease patients having RAND-36 or SF-36 that provided adequate figures for meta-analysis (Watt *et al.*, 2002). This result of meta-analysis has males and females, treated and which were untreated all combined and as shown in Fig. 6. Generally the patients having the FD had scored poorer through the domains as likened to the common population Seven of the studies had reported adequate facts to stratify the result by the ERT treatment status or the gender (Miners *et al.*, 2002; Watt *et al.*, 2010). Pooled SF-36 scores of the 7 studies are shown in Fig. 6.

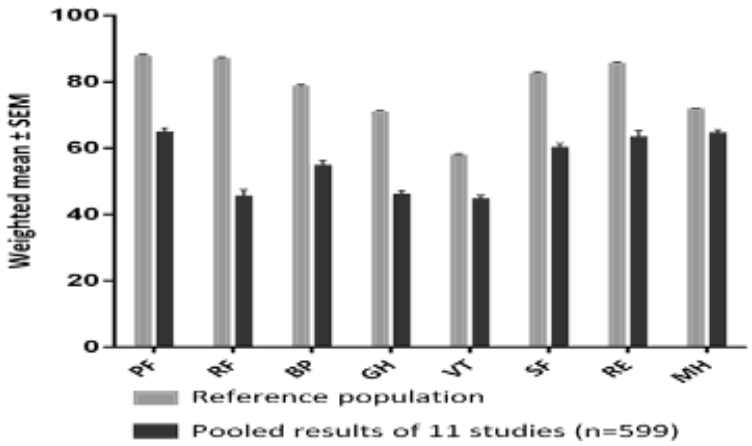

Fig. 6: Pooled results of SF-36

These are the Pooled results, the SF-36 and its subdomain's score. Heavy average and the SEM Resulted from those which were treated and those which were not treated, female and

of male patients. Now the Reference population is driven from the *RP* (role Functioning), *PF* (Physicalfunctioning), *GH* (generalhealth), *BP* (bodypain), *VT* (Vitality), *R E* (role emotional), SF (social functioning), *MH* (Mental Health).Six studies provided the MCS and PCS. The Pooled analysis for the females and the males, and those treated with those untreated patients collectively discovered the weighted or heavy average of MCS and PCS with the value of 42.8 (SEM: 0.62) and 48.7 (SEM: 0.52) respectively (Wilcox *et al.*, 2008).

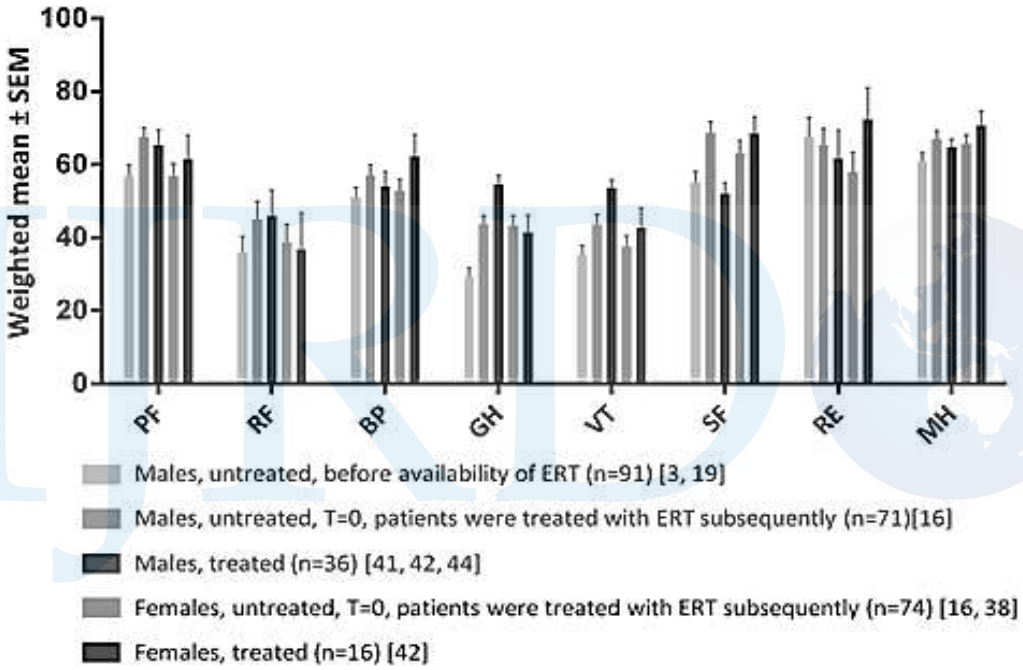

Fig 7: The Pooled results showing SF-36 subdomain score stratified by the treatment and the gender status.

As a total seven studies castoff EQ-5D and compared QoL in the patients having FD to common population. In two of these studies 'average' EQ-5D service scored 0.66 (Hoffman *et al.*, 2005) and 0.56 (Miners *et al.*, 2002). The very first report was made as in varied cohort which consisted of both the females and the males either were treated or were not treated whereas the second comes from pre-ERT time and then only the male patients got studied. The recorded results were ominously poorer than the common population as one of

these two studies have reported an assessed difference of −0.23 (Hoffman *et al.,* 2005). The 3rd report then related an average variance of −0.24 in as collective unit or cohort of those treated and those untreated female and male patients as linked to the common population as well as a, substantial, difference .Two of the studies mentioned the 'EQ-5D' result was lesser in unit or cohort of the 'mainly treated patients which were male' and the unit of treated patients which were female exclusive of specifying exact data. Conclusively, two other studies described that 'EQ-VAS' results in the varied cohorts of the 21 and 33 treated and untreated patients of fabry disease, that were notably lesser as compared with common population as well as accorded controls. Then one study castoff BPI interference score for measuring pain that was related to QoL in female as well as male patients having the FD as untreated or as treated. As Linked to the gender plus age fit the healthy controls and have scored notably poorer (0.4 versus 2.0) In addition to this, many studies have suggested 'a adverse impact of the Fabry Disease' on this QoL. However, no evaluation was made with reference population.

10.0 **Conclusion**

Timely diagnosis in Fabry disease is essential to provide suitable treatment, that is now focused on ERT. It signifies an important landmark in managing of the Fabry disease. It is significant to determine treatment strategies and the therapeutic areas for numerous victim populations to cope outlooks and to provide assistance in the assessment of results got by ERT in the clinical rehearsal atmosphere. The potential alteration in the antigenicity between two official drugs and effect of antibodies on these clinical replies have not been decisively focused. Until such these issues get resolved, clinical replies endure a better marker than the biochemical variations while evaluating these responses to ERT.

References

Anderson, W. (1898). A case of "Angeio-keratoma". *Br. J. Dermatol.*, 10: 113-117.

Barbey, F., Brakch, N., Linhart, A., Rosenblatt-Velin, N., Jeanrenaud, X. and Qanadli, S. (2006). Cardiac and vascular hypertrophy in Fabry disease: evidence for a new mechanism independent of blood pressure and glycosphingolipid deposition. *Arterioscler. Thromb. Vasc. Biol*., 26: 839–844.

Brady, R.O., Uhlendorf, B.W. and Jacobson, C.B. (1971). Fabry's disease: antenatal detection. *Science*., 172: 174-175.

Buechner, S., Moretti, M., Burlina, A.P., Cei, G., Manara, R.A. and Ricci, R. (2008). Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study. *J. Neurol. Neurosurg. Psychiatry*., 79: 1249–1254.

Charrow, J. (2009). A 14-year-old boy with pain in hands and feet. *Pediatr. Ann*., 38: 190-192.

Desnick, R.J., Ioannou, Y.A. and Eng, C.M. (2001). Alpha-galactosidase A deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds, The Metabolic and Molecular Bases of Inherited Disease. *New York, McGraw-Hill.*, 37–74.

Eng, C.M., Germain, D.P., Banikazemi, M., Warnock, D.G., Wanner, C., Hopkin, R.J., Bultas, J., Lee, P., Sims, K., Brodie, S.E., Pastores, G.M., Strotmann, J.M. and Wilcox, W.R. (2006). Fabry disease: guidelines for the evaluation and management of multiorgan system involvement. *Genet. Med*., 8: 539-548.

Fabry, J. (1898). Ein Beitrag zur Kenntnis der Purpura haemorragica nodularis (Purpura papulosa hemorrhagica Hebrae). *Arch. Dermatol. Syphilol.*, 43: 187-200.

Frustaci, A. and Chimenti, C. (2007). Images in cardiovascular medicine. Cryptogenic ventricular arrhythmias and sudden death by Fabry disease: prominent infiltration of cardiac conduction tissue. *Circulation*., 116: 350–351.

Furukawa, K., Iwamura, K. and Uchikawa, M. (2000). Molecular basis for the p phenotype. *J. Biol. Chem.*, 275: 37752–37756.

Germain, D.P. (2002). Fabry's disease (alpha-galactosidase-A deficiency): physiopathology, clinical signs, and genetic aspects. *J. Soc. Biol*., 196: 161-173.

Germain, D.P. (2010). Fabry disease. *Orphanet J. Rare Dis.*, in press.

Hilz, M.J., Stemper, B. and Kolodny, E.H. (2000). Lower limb cold exposure induces pain and prolonged small fiber dysfunction in Fabry patients. *Pain.*, 84: 361-365.

Hoffmann, B., Beck, M., Sunder-Plassmann, G., Borsini, W., Ricci, R. and Mehta, A. (2007). Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy – a retrospective analysis from the Fabry Outcome Survey. *Clin. J. Pain*., 23: 535–542.

Hopkin, R.J., Bissler, J., Banikazemi, M., Clarke, L., Eng, C.M., Germain, D.P., Lemay, R., Tylki-Szymanska, A. and Wilcox, W.R. (2008). Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry. *Pediatr. Res*., 64: 550-555.

Kampmann, C., Wiethoff, C.M., Whybra, F.A., Bachner, E., Mengel and Beck. M. (2008). Cardiac manifestations of Anderson-Fabry disease in children and adolescents. *Acta Paediatr*., 97: 463–469.

Keilmann, A., Hajioff, D. and Ramaswami, U. (2009). Ear symptoms in children with Fabry disease: data from the Fabry Outcome Survey. *J. Inherit. Metab. Dis.*, 32: 739-744.

MacDermot, K.D., Holmes, A., and Miners, .H. (2001). Clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J. Med. Genet*., 38: 750–760.

MacDermot, K.D., Holmes, A., and Miners, A.H. (2008). Clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J. Med. Genet*., 38: 769–75.

Meehan, S.M., Junsanto, T., Rydel, J.J,. and Desnick, R.J. (2004). Renal involvement limited to podocyte pathology and proteinuria in a septuagenarian cardiac variant. *Am. J. Kidney Diseases off J. National Kidney Foundation*., 43: 164–71.

Mehta, A., Ricci, R.,Widmer, U., Dehout, F., Garcia de Lorenzo, A. and Kampmann, C. (2004). Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur. J. Clin. Invest*., 34: 236–242.

Miners, A., Holmes, A., Sherr, L., Jenkinso, C. and MacDermot, K.D. (2002). Assessment of health-related quality-of-life in males with Anderson Fabry disease before therapeutic intervention. *Qual Life Res An Int. J. Qual Life Aspects Treatment*. *Care Rehabilitation*., 11: 127–33.

Miners, A., Holmes, A., Sherr, L., Jenkinson C. and MacDermot, K. (2001). Qual Life Res An Int. J. Qual Life Aspects Treatment. *Care Rehab*ilitation., 11: 127–33.

Monserrat, L., Gimeno-Blanes, J.R., Marin, F., Hermida-Prieto, M. and Perez, I. (2007). Prevalence of fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* 50: 2399–2403.

Nakao, S., Takenaka, T., Maeda, M., Kodama, C., Tanaka, A., and Tahara, M. (1995). An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N. Engl. J. Med*., 333: 288–93.

Ohshima, T., Murray, G.J. and Swain, W.D. (1997). α-Galactosidase A deficient mice: a model of Fabry disease. *Proc. Natl. Acad. Sci. USA.*, 94: 2540–2544.

Orteu, C.H., Jansen, T., Lidove, O., Jaussaud, R., Hughes, D.A. and Pintos-Morell, G. (2007). Fabry disease and the skin: data from FOS, the Fabry outcome survey. *Br. J. Dermatol*., 157: 331–337.

Pintos-Morell, G. and Beck, M. (2009). Fabry disease in children and the effects of enzyme replacement treatment. *Eur. J. Pediatr*., 168: 1355–1363.

Ramaswami, U., Stull, D.E., Parini, R., Pintos-Morell, G., Whybra, C., and Kalkum, G. (2012). Measuring patient experiences in Fabry disease. *validation of the Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ) Health Qual Life Outcomes*., 10: 116.

Ries, M., Clarke, J.T. and Whybra, C. (2006). Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics*.,118: 924–932..

Rombach, S.M., Smid, B.E.,. Bouwman, M.G., Linthorst, G.E., Dijkgraaf M.G., and Hollak, C.E. (2013). Long term enzyme replacement therapy for Fabry disease. *Orphanet J. Rare Dis*., 8: 47.

Schiffmann, R., Kopp, J.B., Austin, H.A., Sabnis, S., Moore, D.F. and Weibel, T. (2001). Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *J.A.M.A*., 285: 2743-2749.

Terryn, W., Poppe, B., Wuyts, B., Claes, K., Maes, B. and Verbeelen, D. (2008). Two-tier approach for the detection of alpha-galactosidase A deficiency in a predominantly female haemodialysis population. *Nephrol. Dial. Transplant*., 23: 294–300.

Watt, T., Burlina, A.P., Cazzorla, C., Schonfeld, D., Banikazemi M., and Hopkin, R.J. (2010). findings from the Fabry Registry. *Genet. Med*., 12: 703–12.

Weidemann, F., Niemann, M., Stork, S., Breunig,F., Beer, M., and C., Sommer. (2013). Long-term outcome of enzyme-replacement therapy in advanced Fabry disease. *J. Intern. Med*., 274: 331–41.

Whybra, C., Miebach, E. and Mengel, E. (2009). A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. *Genet. Med.*, 11: 441–449.

Wilcox, W.R., Oliveira, J.P. and Hopkin, R.J. (2008). Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Mol. Genet. Metab.*, 93: 112–128.

Wyatt, K., Henley, W., Anderson, L., Anderson, R., Nikolaou, V., and Stein. K. (2012). A longitudinal cohort study of people with lysosomal storage disorders. *Health Technol. Assess*., 16: 1–543.

Zarate, Y.A. and Hopkin, R.J. (2008). Lysosomal storage disease. Fabry's disease. *Lancet.*, 372: 1427.