Annals of Hypertension

Review Article
Published: 17 Sep, 2018

# Cardiovascular Disease and Hypertension in Lysosomal Diseases

*Giner-Galvañ Vicente*, Vicente-Navarro David, Sanz-García Javier and Esteban-Giner María Jose*

*Department of General Internal Medicine, Hospital Mare de Déu dels Lliris, Spain*

## Abstract

Recent obtention of different specific drugs for the management of Gaucher disease and Fabry disease, the two more prevalent lysosomal storage diseases, in the last years, is changing the interest form just those clearly related manifestations to another new emergence tones. Information is very scarce, although it seems that, probably as a consequence of macrophages activation secondary to lysosomal deposit, cardiovascular events are a main determinant of life expectancy in both entities. Cardiovascular events in gaucher disease are related to an increased insulin resistance status, and in Fabry disease there is a direct endothelial deposit with special protagonism for kidney function deterioration. In this increased cardiovascular risk ambient it is highly surprising the absence of basic information about blood pressure. Probably it is now time to take care on blood pressure and some other basic aspects of general health in these complex entities in parallel with the obtention and improvement of new specific drugs and pharmacological strategies.

## Introduction

Gaucher Disease (Gd) and Fabry Disease (FD) are both the most prevalent Lysosomal Storage Diseases (LSD), although with a very low prevalence among the general population, belonging to the so-called rare diseases, a group of processes present in a very low proportion in the population, and usually genetically determined [1]. They are both characterized by a genetically determined decrease activity of some enzymes in the lysosome: beta-glucorerebrosdie in Gd, and alpha-galactosidase in FD. As a consequence, accumulation of some different substances in the lysosomes of different tissues in the body develops. Because of this mechanism, this kind of inherited processes has also been known as lysosomal storage diseases [2].

The pathophysiological effect of the genetically determined enzyme defect is not just the result of the local mechanical deposit [3-5]. Because the macrophages are the main cells regulating inflammation and other cellular processes as oxidative stress, in the last years it has been demonstrated an increased inflammatory state in those individuals with lysosomal storage diseases. This increased inflammatory state explains systemic effects that sometimes are independent of the amount of the lysosomal overload. As an example, in a recent study with 107 patients with FD and Pompe disease, it has been demonstrated an inverse relationship between cerebral artery diameter and enzyme activity. Similarly to most new findings in LSD, it is difficult to explain from a pathophysiological point of view, this finding, although a possibility is that a defect in the enzymes could create an interference with the physiological vasoregulation and probably inducing a prothrombotic ambient explaining the increased tendency for stroke in FD [6].

The development in the last years of different pharmacological treatments for LSD, and especially for Gd and FD, has changed the situation of patients and the way to understand and manage these conditions [4,7]. As previously with HIV infection or diabetes, for patients with GD and FD the access to different effective drugs has increased the life span of the affected patients. This potential improvement in life expectancy has two direct consequences. On one hand, the chronification of the disease gives the opportunity to observe new emergent manifestations previously not considered in this kind of patients because of a lack of time for the evolution of these complications. On the other hand, we do not know the long-term effects of new orphan drugs. However, nowadays it is noteworthy the absence of information about basic aspects of such new potential manifestations in these entities, although some evidence underscores the importance of Cardiovascular (CV) processes in GD and FD as representative of LSD inherited defects.

OPEN ACCESS

***Correspondence:***
*Giner-Galvañ Vicente, Department of Internal Medicine, Hospital Mare de Déu dels Lliris, Alcoy (Alicante), Spain, Tel: 34680588421; E-mail: giner_vicgal@gva.es*

**Received Date**: *22 Aug 2018*
**Accepted Date:** *15 Sep 2018*
**Published Date:** *17 Sep 2018*

***Citation:***
*Vicente G-G, David V-N, Javier S-G, María Jose E-G. Cardiovascular Disease and Hypertension in Lysosomal Diseases. Ann Hypertens. 2018; 1(2): 1008.*

## Cardiovascular Disease in Lysosomal Diseases

An evident strategy to assess the relevance of CV disease in LSD processes can be the review of their natural evolution. But we do not have such basic information as a consequence of different reasons common for all rare diseases [8,9]. The first and most difficult to overcome reason is their low prevalence in the general population. A second reason for the scarcity of information is that traditionally for rare diseases, more life-threatening aspects have received all the attention until now, when the availability of different specific and effective treatments is improving survival with the possibility to analyse potential emergent aspects of these diseases as quality of life or emergent pathologies. A third limitation, when highly prevalent conditions in the general population like hypertension or Cardiovascular (CV) events are considered for rare diseases, is that it is very difficult to distinguish if in the case of a relationship is found, it is a casual (epidemiological relationship) or causal (pathophysiological) relationship.

When Gd is considered, only two studies about the natural evolution of the disease have been published, one in non-treated patients, and the second in patients treated with enzyme infusions [10,11]. Considering the quality of the evidence, it should be underscored that one of the publication is a retrospective one and the other one is an estimation considering general US population [10,11]. Another methodological limitation is the very low number of events, with 184 and 102 patients with known cause of death in each publication respectively [10,11]. Weinreb et al., [11] published in the year 2008 a comparison of the life span of 2,876 patients with type 1 Gd (>85% treated during 5 years to 6 years with alglucerase or imiglucerase) from the International Gaucher Registry compared with that of the general US population. They estimated a shorter life span for patients with Gd (68 years *vs.* 77 years) with a very high heterogeneity in the specific cause of death. CV diseases were the main cause of shorter life with a double incidence compared to general population (13% *vs.* 6%). More interestingly, it was also described an earlier incidence of global CV dead (58 years *vs.* 81 years) as well as for stroke related mortality (64 years *vs.* 82 years). In the retrospective publication with untreated patients from the Pittsburgh Registry, similar results were obtained, although the preponderance of CV disease was lower. After global consideration of the results of both studies it is quite difficult to obtain a clear conclusion, although it seems that CV death is a common cause of mortality in Gd. On the other hand it can also be considered the potential negative effect of enzyme replacement taking into account the different relevance of CV diseases as a cause of mortality in the presence or absence of this treatment and its potential for the activation of immunological reactions [12].

More robust information is available for FD, its natural history and associated cardiovascular events. In fact, the main manifestations of the disease are protein uric chronic renal failures, hypertrophic miocardiopathy, and stroke. The evidence is as strong that can be considered a "cardiovascular disease" by itself [13]. As previously commented for Gd, data from the FOS (Fabry Outcome Survey) registry show a shorter life span for patients with fed compared to the general population (58 years *vs.* 75 years for men, and 75 years *vs.* 80 for women), with a clear preponderance of CV disease as the main cause of mortality, and a main protagonist for chronic kidney disease, as illustrated by the fact that 60% of patients with cardiovascular disease had previously been on haemodylisis [14-16].

Admitting the limited quality of the existing evidence, it seems that CV disease is relevant with complications in FD and Gd. As previously stated, the actual doubt is if this relationship is merely an epidemiological (casual) or pahthophysiological (causal) one.

## Systemic Hypertension in Lysosomal Storage Diseases

Persistently increased Blood Pressure (BP) is a well-known risk factor for CV events, and because its high prevalence in the worldwide population, can be considered the main determining of the actual charge of CV disease all around the world [17]. If CV disease is relevant in LSD, knowledge about BP and its control in such population can also be a strategy to improve the future evolution of patients with these diseases. However, the information that nowadays we have about BP in rare diseases and LSD ones is very scarce, especially for Gd.

Despite the central role of nephropathy in FD, specific information about systemic BP is very scarce and confusing. In the opinion of some authors, systemic hypertension prevalence is lower than that reported for other forms of proteinuric chronic kidney disease, with in some cases tendence to hypotension due to dysautonomic vascular control [18]. However, in a descriptive transversal study with 390 patients again from the FOS registry by J Kleinert, elevated BP was present in 54% and 47% of men and women with FD [19]. However, it has to be considered that high BP was defined as office BP values higher than 130 mmHg/80 mmHg. As for its prevalence, the information about how to manage elevated BP in FD is also very scarce, although a direct relationship has been described between BP values and development of miocardiopathy and chronic kidney disease, including those patients with normal BP values [18,20]. Increased BP mechanisms in the FD are unknown, and probably multifactorial. The initial phenomenon is likely the GB3 vascular endothelial deposit producing the activation of the local rennin-angiotensin system, and, as direct consequence, local inflammatory and oxidative phenomena as well as increased arterial stiffness and BP increase [21].

Nowadays, any specific study has been made in FD to know how to manage BP in these patients. The recommendations have been made by authors just applying evidence obtained from the general population, with a main relevance for the control of proteinuria. The general therapeutical target is to reduce proteniuria to less than 500 mg/day. To obtain this objective, BP and hyperlipidemia control has been recommended, although we do not have evidence to establish a clear therapeutical target [22]. Because enzyme replacement therapy just slows the kidney deterioration, and the well-known anti-proteinuirc effect of these drugs, is has been recommended the systematic use of Angiotensin Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) to reduce proteinuria with or without increased BP values when an increased urinary albumin/protein excretion is present [23-25]. The addition of amiloride to patients with a previous double rennin-angiotensin blockade with ACEI plus ARB has demonstrated additional antiproteinuric effect [26]. Although all the authors are in accordance with this recommendation, it is noteworthy the low grade of the existing evidence: the recommendation for the use of amiloride is based in just one case report, and the recommendation for the use of ACEIs and ARBs is based in one post hoc study with ten patients and one open label non-randomized prospective study with 11 normotensive and

hypertensive participants [24-26]. It has been demonstrated that BP values <130 mmHg as recommended for proteinuric chronic kidney disease is well tolerated, although some hypertensive symptoms can be present and easily reversed after ACEI or ARB dose reduction [25].

When Gd is considered, we have previously indicated that information is again very poor and scarce, although indicative that cardiovascular disease probably has a main role as a determinant of mortality [10,11]. Because the poor quality of the existing evidence as well as high prevalence of CV events in the general population, the existence of a reasonable pathophyisiological mechanism is a strong factor in favor of the existence of a "real" or causal instead of casual relationship [27]. And it is the case for Gd, in which the Langeveld's group has demonstrated with the euglucemic hyperinsulinemic clamp an increased insulin resistance state compared with healthy volunteers [28]. This increased insulin resistance has been demonstrated to be the consequence of the deposit of GM3 (monosialodihexosylgangliosid), an increased glucoesphingolipid, in insulin receptor [29]. In favor of insulin resistance as the cause of an increased cardiovascular risk, it has also described characteristic lipid alterations as well as increased incidence of cholesterol gall bladder litiasis, both traditional components of the insulin resistance syndrome that are corrected with specific treatment for Gd [12]. Hypertension is also a well-recognized component of insulin resistance syndrome. For this reason it seems to be normal to have specific information about BP in Gd. But the reality is that no paper has been published about BP in Gd. As a consequence, the actual recommendation would be to extend those for general population to these patients. In favor of the need for specific information for LSD is the quite different impact on renal function when comparing FD and Gd. In FD the most important organic impact is on the kidney, however, in Gd it seems that kidney disease is not related to Gd but associated comorbidity [30].

## Conclusion

Due to its low prevalence in the general population, it is very difficult to obtain high-quality evidence about any aspects in rare diseases. The recent obtention of different specific pharmacological drugs for the treatment of Gd and FD probably will change the natural history of these diseases as a consequence of its chronification, being now the time to look for other than traditionally related aspects of these diseases, as has been the case for HIV infections, diabetes and other chronic entities.

Actually available, and very low quality data, indicate that both for Gd and Fd CV disease is an important determinant of life expectancy and quality of life. Probably, it is now time to study basic aspects of systemic BP and other traditional cardiovascular risk factors in Gd and FD. It is not reasonable to spend a lot of money with orphan drugs and disattend some other basic aspects of a cardiovascular healthy life. It is also necessary to analyze long-term effects of some new specific treatment for these LSD.

## References


1. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. International Society for Pharmacoeconomics and Outcomes Research Rare Disease Special Interest Group. Rare disease terminology and definitions. A systematic global review: Report of the ISPOR Rare Disease Special Interest Group. Value Health. 2015;18(6):906-14.
2. Coutinho MF, Matos L, Alves S. From bedside to cell biology: a century of history on lysosomal dysfunction. Gene. 2015;555(1):50-8.
3. Rigante D, Cipolla C, Basile U, Gulli F, Savastano MC. Overview of immune abnormalities in lysosomal storage disorders. Immunol Lett. 2017;188:79-85.
4. Klein AD, Futerman AH. Lysosomal storage disorders: old diseases, present and future challenges. Pediatr Endocrinol Rev. 2013;11(1):59-63.
5. Bajaj L, Lotfi P, Pal R, di Ronza A, Sharma J, Sardiello M. Lysosome biogenesis in health and disease. J Neurochem. 2018.
6. Shah H, Liong C, Levy OA, Waters C, Fahn S, Marder K, et al. Association of low lysosomal enzymes activity with brain arterial dilatation: A pilot study. Stroke. 2018.
7. Ortolano S, Viéitez I, Navarro C, Spuch C. Treatment of lysosomal storage diseases: recent patents and future strategies. Recent Pat Endocr Metab Immune Drug Discov. 2014;8(1):9-25.
8. Kempf L, Goldsmith JC, Temple R. Challenges of developing and conducting clinical trials in rare disorders. Am J Med Genet A. 2018;176(4):773-83.
9. Bharmal M, Guillemin I, Marrel A, Arnould B, Lambert J, Hennessy M, et al. How to address the challenges of evaluating treatment benefits-risks in rare diseases? A convergent mixed method approach applied within a Merkel cell carcinoma phace 2 clinical trial. Orphanet J Rare Dis. 2018;13:95.
10. Weinreb NJ, Barbouth DS, Lee RE. Causes of death in 184 patients with type 1 Gaucher disease from the United States who were never treated with enzyme replacement therapy. Blood Cells Mol Dis. 2018;68:211-7.
11. Weinreb NJ, Deegan P, Kacena KA, Mistry P, Pastores GM, Velentgas P, et al. Life expectancy in Gaucher disease type 1. Am J Hematol. 2008;83(12):896-900.
12. Giner V. [Comorbidity in Gaucher's disease.] Facts & Research. 2012;79.
13. Baig S, Vijapurapu R, Alharbi F, Nordin S, Kozor R, Moon J, et al. Diagnosis and Treatment of the Cardiovascular Consequences of Fabry Disease. QJM. 2018.
14. Mehta A, Clark JTR, Giugliani R, Elliott P, Linhart A, Beck M, et al. FOS Investigators. Natural course of Fabry diseases: changing pattern of causes of death in FOS. The Fabry Outcome Survey. J Med Genet. 2009;46(8):548-52.
15. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med. 2009;11(11):790-6.
16. Talbot AS, Lewis NT, Nicholls KM. Cardiovascular outcomes in Fabry disease are linked to severity of chronic kidney disease. Heart. 2015;101(4):287-93.
17. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. NCHS Data Brief. 2017;289:1-8.
18. Jain G, Warnock DG. Blood pressure, proteinuria and nephropathy in Fabry disease. Nephron Clin Pract. 2011;118(1):43-8.
19. Kleinert J, Dehout F, Schwarting A, de Lorenzo AG, Ricci R, Kampmann C, et al. Prevalence of uncontrolled hypertension in patients with Fabry disease. Am J Hypertens. 2006;19(8):782-7.
20. Krämer J, Bijnens B, Störk S, Ritter CO, Liu D, Ertl G, et al. Left ventricular geometry and blood pressure as predictors of adverse progression of Fabry cardiomyopathy. PLoS One. 2015;10(11):0140627.
21. Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE. Vasculopathy in patients with Fabry disease: current controversies and research directions. Mol Genet Metab. 2010;99(2):99-108.
22. Del Pino M, Andrés A, Bernabéu AÁ, de Juan-Rivera J, Fernández E, de Dios García Díaz J, et al. Fabry Nephropathy: An Evidence-Based Narrative Review. Kidney Blood Press Res. 2018;43(2):406-21.

23. Weidemann F, Niemann M, Störk S, Breunig F, Beer M, Sommer C, et al. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J Intern Med. 2013;274(4):331-41.

24. Tahir H, Jackson LL, Warnock DG. Antiproteinuric therapy and Fabry nephropathy: sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-beta. J Am Soc Nephrol. 2007;18(9):2609-17.

25. Warnock DG, Thomas CP, Vujkovac B, Campbell RC, Charrow J, Laney DA, et al. Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy. J Med Genet. 2015;52(12):860-6.

26. Trimarchi H, Forrester M, Lombi F, Pomeranz V, Raña MS, Karl A, et al. Amiloride as an alternate adjuvant antiproteinuric agent in Fabry disease: The potential roles of plasmin and uPAR. Case Rep Nephrol. 2014;2014:854521.

27. Nascimbeni F, Dalla Salda A, Carubbi F. Energy balance, glucose and lipid metabolism, cardiovascular risk and liver disease burden in adult patients with type 1 Gaucher disease. Blood Cells Mol Dis. 2018;68:74-80.

28. Langeveld M, Ghauharali KJ, Sauerwein HP, Ackermans MT, Groener JE, Hollak CE, et al. Type I Gaucher disease, a glycosphingolipid storage disorder, is associated with insulin resistance. J Clin Endocrinol Metab. 2008;93(3):845-51.

29. Ghauharali-van der Vlugt K, Langeveld M, Poppema A, Kuiper S, Hollak CE, Aerts JM, et al. Prominent increase in plasma ganglioside GM3 is associated with clinical manifestations of type I Gaucher disease. Clin Chim Acta. 2008;389(1-2):109-13.

30. Becker-Cohen R, Elstein D, Abrahamov A, Algur N, Rudensky B, Hadas-Halpern I, et al. A comprehensive assessment of renal function in patients with Gaucher disease. Am J Kidney Dis. 2005;46(5):837-44.