Lysosomal Storage Diseases Brazil Network, helping Brazil and Latin America to identify LSD patients: Report on the first 10 years of activity

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Abstract

To contribute to the diagnosis of lysosomal storage diseases (LSDs), an innovative program called LSD Brazil Network (LBN) was implemented to provide information and testing of high-risk patients, free of charge, to doctors and services from Brazil and other countries. This paper describes the structure, services provided, and results obtained by LBN in its first 10 years of operation. The LBN has a core group which is responsible for the operation, guidance, logistics of sample collection and transportation, test reports and informative materials. The diagnostic investigation is performed in several laboratories affiliated to the program, all located in Porto Alegre, Brazil. The first ten years of operation of the LSD Brazil Network (2013–2022) were reviewed in detail. Along 10 years, 26,489 patients were investigated by the LBN, with the diagnosis of 27 LSDs confirmed in 1,320 cases (4.98%). Comparing the first period of 5 years with the second one, there was a decrease in the number of requests, probably reflecting the impact of the Covid-19 pandemics. Interestingly, the same comparison indicates that there was an increase of 46% in the rate of diagnosis, possibly due a better selection of suspected cases. The model developed by the LSD Brazil Network, aiming to increase awareness and to remove barriers to diagnostic tests, suggests that the implementation of reference networks seems to be a suitable alternative to foster the diagnosis of LSDs, especially in developing countries, where resources and facilities are scarce.

INTRODUCTION

Most developing countries face difficulties to offer diagnostic tests for genetic diseases, due to the high complexity of many procedures, low individual demand of each specific test, scarce funding to cover the costs and limited reimbursement by public and private health policies (Giugliani et al, 2016).

In the case of lysosomal storage diseases (LSDs), a group of over 70 different conditions (Platt et al, 2018), a well-qualified diagnostic laboratory was implemented at the Medical Genetics Service of Hospital de Clinicas de Porto Alegre, in South Brazil. Planned to deal with the local demand, the laboratory soon became an informal reference center for Brazil and the region.

In due course, it was designed a sustainable project (LSD Brazil Network) to offer diagnostic services at no cost for high-risk patients referred by doctors and services associated to the diagnostic network.

This paper describes the structure, services provided, and results obtained in the first 10 years of operation of the LSD Brazil Network.

ORIGINS OF THE LSD BRAZIL NETWORK

In 2004 we decided to organize the huge demand that our diagnostic laboratory at HCPA was receiving for tests related to the suspicion of Mucopolysaccharidoses (MPS) coming from all parts of Brazil, and we created the MPS Brazil Network (Federhen et al, 2020). To run this program, we set up an administrative office to raise and manage funds, deal with the information and diagnostic requests, and
send the reports. With the funds obtained (research grants from governmental agencies and unrestricted grants from private companies) we managed to support the acquisition/maintenance of equipment, purchase reagents and other consumables, and pay fellowships for the personnel involved in the project. This is a very successful program which results were already published (Josakian et al, 2021).

Inspired on the MPS network and needing to deal with the specificities of the diagnosis of Niemann-Pick disease type C, which at that time required skin biopsy and cell culture for the Filipin testing, we created in 2009 a very specific project, the NPC Brazil Network. This project was also very successful, having diagnosed hundreds of NPC patients in Brazil and other countries. It remained active until the emerging biomarkers were consolidated and able to replace the Filipin test as initial testing method, making NPC a disease which can be screened by standard technology along other LSDs (Kubaski et al, 2022).

With these models in mind, we decided to create, by the end of 2012, the LSD Brazil Network (LDN), keeping the operational template of the MPS and NPC networks, and incorporating all LSDs under its umbrella.

THE OPERATIONAL MODEL OF THE LSD BRAZIL NETWORK

The LBN has a core group which is responsible for the operation, including fund raising and resources administration, creation and maintenance of the website, operation of the toll-free telephone line and WhatsApp business account. This group provides guidance about the program by phone, email and WhatsApp, deals with the logistics of sample collection and transportation, and for providing the test reports. Also produces material to increase awareness and education, as booklets for patients and a quarterly newsletter.

The requests for investigation come from doctors who are affiliated to the LBN, who suspect the possibility of LSD in a specific patient. They must send a form with clinical/laboratory information about the index patient, and a signed informed consent form, along the appropriate samples (in most cases, blood and/or urine). No fee is charged for the tests, and the cost of sample transportation is reimbursed by the LBN whenever needed.

The diagnostic investigation is performed in several laboratories affiliated to the program, all located in Porto Alegre, Brazil. These laboratories receive human resources, reagents and other consumables, and donation/maintenance of equipment. When the investigation is completed, the requesting doctor can access a detailed report in the restricted area of the website.

The program is maintained by research grants from Brazilian governmental agencies and unrestricted grants from private companies. The core group produces monthly reports to the sponsors with the number of requests and number of confirmed diagnosis (without any patient identified data).

Figure 1 illustrates the mode of operation of the LSD Brazil Network.
RESULTS OBTAINED BY LSD BRAZIL NETWORK

The first ten years of operation of the LSD Brazil Network (2013–2022) were reviewed in detail and are presented here. We also compared the first period of five years (2013–2017) with the second period five years (2018–2022).

Table 1 shows the number of requests by year from 2013 to 2022, the number of confirmed diagnoses, the rate of diagnosis.

Table 2 shows the number of cases of each LSD identified in the 2013–2022 period, with the numbers indicated also by five-year period (2013–2017 and 20218 – 2022).

Figure 2 indicates the number of LSD cases diagnosed, according to the country of origin.

Figure 3 shows the mean age at diagnosis for the 10 most frequent conditions diagnosed, comparing the age observed in the period 2013–2027 with that observed in the period 2018–2022.

DISCUSSION

LSDs represent a diagnostic challenge, due to its individual rarity, overlapping features and need of specialized tests to confirm the diagnosis (Kingma et al, 2015).

Although genetic testing brings a huge contribution to its identification, at least in the field of LSDs, biochemical procedures are still needed due to the high proportion of variants of unknown significance and to prove that genetic variations eventually found have a biological consequence in vivo (Filocamo and Morrone, 2011)

In due course, reference services for an integrated laboratorial approach to LSDs are needed. In addition of being able to provide specialized testing services, the reference laboratories have the opportunity of accumulating experience with diagnoses of ultra-rare conditions, which would not be possible if the tests are spread among many laboratories (Vieira et al, 2019).

Along the 10 years covered in this report, 26,489 patients suspected of having a LSD were investigated by the LBN, with the diagnosis of 1,320 cases of 27 different LSDs (diagnosis rate of 4.98%). We observed that the overall number of requests for investigation decreased by 37% from the first 5 period of 5 years (2013–2017) to the second period of five years (2018–2022), which may reflect the impact of Covid-19, that affected the provision of elective medical procedures and logistics in general. However, the decrease on the number of cases diagnosed, when comparing one five-year period with the other, was limited to 8%. Interestingly, there was an increase of 46% in the rate of diagnosis when period 2013–2017 is compared with the period 2018–2022, possibly indicating a better selection of suspected cases, tentatively related to the educational initiatives of the LBN and other groups along the years.
Interestingly, the seven most frequent conditions diagnosed (Gaucher, MPS II, MPS IVA, MPS VI, MPS I, CLN2 and ASMD) are diseases which have specific therapies available, potentially reflecting a higher awareness of the rare disease community about treatable conditions (de Dios Garcia-Diaz, 2022). Among the diseases that have also a significant number of diagnoses but still do not have specific therapies available, we highlight Krabbe, GM2 Gangliosidosis (Tay-Sachs, including B1 variant), and MPS IIIB, completing the group of the ten most frequent LSDs identified, all with more than 50 cases identified in the period 2013–2022. Despite having no approved therapies so far, these last three conditions have very active patient advocacy groups, which promote awareness on the diseases. We believe that Fabry and Pompe diseases are underrepresented in this survey, possibly by the fact that their diagnosis is also provided by other laboratories in Brazil.

Comparing the age at diagnosis in the period 2013–2017 with that observed in the period 2018–2022 for the 10 most frequent conditions diagnosed, we observed a trend to decrease for Mucopolysaccharidosis types I, IVA, and IIIB, GM2 Gangliosidosis – Tay-Sachs, Gaucher disease, and Neuronal Ceroid Lipofuscinosis type 2, potentially indicating a higher awareness of the community about these diseases. For Mucopolysaccharidosis types II and VI, Acid Sphingomyelinase Deficiency and Krabbe disease, however, there was an increase in the mean age at diagnosis in the last 5 years. Having a closer look on this (data not shown), we realized that this increase was driven by a few cases diagnosed later in life. We speculate that, for these conditions, the identification of several cases belonging to the attenuated end of the spectrum may be also attributed to an increased awareness about these diseases.

CONCLUSIONS

The implementation of reference laboratories seems to be a suitable alternative to foster the diagnosis of LSDs, a group of rare conditions (most of them, in fact, ultra-rare) which demand a specialized service to provide a reliable diagnosis. This is especially true for developing countries, where resources and facilities are scarce. The model developed by the LSD Brazil Network, aiming to increase awareness and to remove barriers to diagnostic tests, enabled the identification of 1,320 cases of 27 different LSDs along 10 years, making possible that specific therapies were implemented in most of these cases. In addition, the decrease of the mean age at diagnosis, observed in several treatable conditions, may lead to better treatment outcomes.

Declarations

CONFLICTS OF INTEREST

The authors inform that they do not have conflicts of interest relevant to this manuscript.

Author Contribution

Acknowledgement

Program approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (#2003-0666 and #2017-0664).

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Data Availability

The data reported here were collected in a project approved by the institutional ethics committee, and stored in a restricted access database. All patient identification was removed during data extraction and analysis.

References

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Figures
Illustrative scheme of the operational routine of the LSD Brazil Network.

Figure 2

Origin of LSD cases diagnosed, according to the country.
Figure 3

Mean age at diagnosis for the 10 most frequent conditions diagnosed, comparing the age observed in the period 2013-2027 with that observed in the period 2018-2022.