The Prevalence and Mutation Profile of Southern African Patients with Treatable Lysosomal Storage Disorders.

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1. Introduction:

Lysosomal storage disorders (LSD's) are a group of disorders characterized by progressive accumulation of substrate accumulation in the lysosomes, eventually leading to organ dysfunction and failure.[1] There are more than 40 specific disorders in the group and each is due inherited mutations in a specific lysosomal enzyme. Each disorder is thus due to consequences of the type of substrate that is not metabolised and then accumulates in a variety of tissues.[2] Most are inherited in an autosomal recessive pattern but a few are X-linked.[3] Collectively the incidence is 1/7700 to 1/10000 births but individually some occur in less than 1per million. Some types are more frequent in certain population groups but they are generally panethnic.[1] Most LSD's usually affect numerous organs with diverse presentations and complications.

Because of the individual rarity, progressive nature, often insidious non-specific onset and involvement of multiple organs, the diagnosis is often only made later in the disease course. Early diagnosis offers the opportunity to prevent irreversible organ damage and improve the quality of life for the affected individual.[1] The majority of LSD's are not treatable but specific enzyme replacement therapies (ERT), substrate reduction therapies or even stem cell replacement are available for certain disorders. Even if not treatable, supportive care and actively addressing complications can have a beneficial effect on the individual's and family's quality of life.

The treatable disorders are Gaucher disease, Fabry disease, Pompe disease, Mucoploysaccharidosis (MPS) type 1 (Hurler and Scheie syndromes), type 2 (Hunter syndrome), Type 4 (Morquio syndrome) and type 6 (Maroteaux-Lamy syndrome).

Gaucher disease is due to glucocerebrosidase deficiency. It is inherited in an autosomal recessive pattern. It occurs in about 1/60000 persons except among the Ashkenazi Jewish descendants where an incidence of 1/450 has been recorded.[4,5] As a result of the enzyme deficiency, there is accumulation of glucocerebroside causing engorgement of the macrophages in bone marrow, spleen, liver and occasionally the lungs. Presentation is usually in the first or second decade. There are 3 types with type

2 causing early childhood deaths and type 3 involving the nervous system. Only type 1 is amenable to treatment.

Pompe disease is due to α-glucosidase deficiency. It is inherited in an autosomal recessive pattern. Glycogen accumulation in the lysosomes of muscle occurs. There are 2 types, one presenting with cardiac failure and death in infancy if not treated and the other at later ages with a myopathy. The overall incidence is 1/40000 but does vary in different population groups.[3,6,7]

Fabry (or Fabry-Anderson) disease is due to α-galactosidase deficiency and is inherited in an X-linked pattern. The incidence is 1/40000 males and 1/117000 individuals.[1,8] The disease presentation is much worse and earlier in males. The clinical presentation includes peripheral neuropathy, hypertrophic cardiomyopathy, renal failure, stroke, skin and corneal involvement. There is globotriaosylceramide (GL-3) accumulation in renal podocytes, cardiac myocytes, vascular endothelium and peripheral nerves. Death can be a result of cardiac, renal or cerebrovascular involvement.[8]

Hurler/Scheie syndromes (MPS1) are due to a deficiency in α-iduronidase and is also inherited in an autosomal recessive pattern. The incidence is about 1/100000.[1] Originally Hurler and Scheie were considered different because Hurler has CNS involvement but are now shown to a spectrum of the same disorder. Presentation is usually in the first year of life but at about 3 years for the attenuated form. Dermatan and heparan sulphate accumulate in connective and soft tissue, joints and cardiac tissue. Corneal deposits, contractures of the fingers and hepatosplenomegaly are characteristic. Death often occurs before adolescence. ERT does not impact the CNS involvement.

Hurler syndrome (MPS2) is due to a deficiency of iduronate-2-sulfatase. It is inherited in an X-linked recessive pattern. The incidence is between 1/100000 and 1/170000 but there are anecdotal opinions that it may be higher in South Africa. Clinically similar to Hurler syndrome except that only boys are affected and there is no corneal involvement.

Morquio A (MPS4A) is due to a deficiency in N-acetylgalactosamine-6-sulfatase. It is inherited in an autosomal recessive pattern. Incidence varies from 1/926000 in Australia, 1/599000 in UK to 1.1872000 in Malaysia. There much clinical overlap with the other MPS's.[9]

Maroteaux-Lamy (MPS6) is due to a deficiency in arylsulfatase B. It is inherited in an autosomal recessive pattern. The incidence appears to be less than 1/240000. There is again much phenotypic variation with similar clinical findings to MPS1.

All of the selected LSD's have been identified in South Africans. No formal studies, to the researcher's knowledge, have been done to determine the incidence or prevalence in South Africa. Apart from 1 article identifying mutations in South African patients with Gaucher disease[10], no formal studies to identify the mutation profile in other LSD's have been undertaken. ERT is available in South Africa and more than 1 product is available for some disorders. ERT is generally very expensive and is administered intravenously weekly or every other week. Substrate reduction therapy and stemcell replacement is also available in South Africa. Some of the medications need a Section 21 application as they are not registered in South Africa.

All of the disorders included in this study frequently present in childhood or have a childhood onset. Infants with the infantile type of Pompe's disease do not survive infancy without treatment. Many children with mucopolysaccharidoses will die in childhood or early adolescence. All of these disorders have a significant impact on the health and quality of life of affected children. The inclusion of minors is thus essential to truly understand the impact of these disorders on children. Including children will also enable more accurate prevalence/incidence data. This will create awareness of these rare disorders in childhood and allow an opportunity to initiate treatment early and achieve improved outcomes. The nature of this study poses minimal, if any, risk for participants.

2. Aim:

The aim of this study is to determine the prevalence of the selected treatable LSD's in Southern Africa. A second aim is to describe the South African mutation profile of these disorders. The pattern of clinical presentation will be a final aim.

3. Research questions:

The following research questions will be addressed in the objectives of this study:

1) How prevalent are the selected LSD's in the different populations of Southern Africa?

2) How are these disorders identified, diagnosed and treated?

3) What is the mutation profile of these disorders in the Southern Africa populations?

4. Objectives of the study:

- Calculate the prevalence of these disorders in Southern Africa. This will help health funders to budget for high cost of treating these disorders.
- To describe the presenting features and age at presentation and diagnosis.
- To describe the mutation profile in Southern Africa.

5. Study design:

This will be a retrospective study of patient files with the purpose of obtaining family, clinical and laboratory data.

6. Methodology:

Treating physicians will be contacted and invited to participate in the study. The treating physicians will be identified by a variety of methods. Because LSD's are multisystem disorders, physician societies will be contacted and the invitation as well as data collection sheets distributed electronically. The societies will be Cardiologists, Neurologists, Nephrologists, Haematologists, Paediatricians in these subspecialities and Medical Geneticists.

The laboratories providing specific enzymatic and genetic analyses for these disorders will be contacted and requested to provide the names of physicians who provided specimens. These physicians will then be contacted directly.

7. Sample:

All patients diagnosed with any of these specific disorders are eligible for inclusion. The inclusion will be dependent on their treating physician's desire to participate as well the patients, or parents', own decision.

8. Measurement:

The treating physician will identify patients who have been diagnosed with one of these disorders and consent to participate by signing consent. They will complete a questionnaire specific for the disorder diagnosed.

The questionnaire will focus on the following aspects: 1) demographic data; including age, gender, race, name and date of birth; 2) family history; 3) Clinical information about presenting symptoms, age at onset of these symptoms, age at diagnosis, complications present; 4) diagnostic information such enzyme activity and mutation if identified; 5) treatment provided and efficacy of treatment.

The questionnaires, physician's consent and patient's, or parent's, consent will be returned to the researcher. Upon receipt, the data will be captured into Excel® spreadsheets; at this stage identifying

data will not be recorded. Once all data has been collected, the spreadsheets will be submitted for statistical analysis. The analysis will be prevalence data and percentages.

9. Methodological and measurement errors:

By approaching numerous physician organisations to identify patients, the researchers intends ensuring, as far as possible, that as many patients as possible will be identified. This will make the data as accurate as possible. Being a retrospective collection of data, some data may not be available.

10. Data analysis:

Statistical calculation will most likely be very basic and only prevalence or percentages calculated. Commercially available statistical software such as SAS or Sequel will be used to analyse the data if the Dept. Biostatistics is unable to assist.

11. Time schedule:

Once approval from the ethics committee has been granted, a 2 month period for contacting the treating physicians and another 3 months for responses to be obtained will be allowed. Thereafter no additional data will be accepted or included.

12. Budget:

As far as possible, contact with treating physicians and obtaining of data will be performed electronically. Expenses will be covered from Division of Clinical Genetics funds as required.

13. Ethical aspects:

Each treating physician will be considered as the research subject. The treating physician will thus provide consent for participating. The treating physician will be expected to obtain informed consent from each patient or parent/legal guardian as well as assent in the case of minors (where applicable). The documents for the consent and assent will be provided.

Because multiple sources of data collection will be utilized, identifying patients is required. This will enable the researcher to combine data sheets when more than 1 set of data per patient is collected. These are inherited disorders and full names and dates of birth are preferable to initials, which may be the same within a family. The names will be not be used when the data is recorded into spreadsheets. This will ensure patient confidentiality. The data will be kept on a password protected computer. At the completion of the study, this data may be stored on encrypted, password protected DVD's.

Participants will not receive any monetary remuneration for study participation. Participants can be included as authors if publishable results are obtained.

No negative effects are anticipated in this retrospective study which will only collect existing information.

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14. Implementation:

This study is expected to provide data about the prevalence of treatable LSD's. This can provide healthcare funders with statistics that can be beneficial in planning and budgeting. Identifying the

mutation profile may identify common South African mutations which can enable laboratories to develop cost-effective analysis techniques for diagnosis in South Africa.

15. References:

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16. Appendices:

- Appendix A – Treating physician consent form
- Appendix B – Patient, parent/legal guardian consent form, assent form for children
- Appendix C – Data collection sheets
- Appendix D – Spreadsheet
- Appendix E - Invitation to participate