Hereditary Calcium Oxalate Stone Disease Registry Planning Meeting
August 9, 2002

Meeting Summary

The planning meeting on creating a registry for hereditary calcium oxalate stone disease was held August 9, 2002, in Boston, Massachusetts. Drs. Chris Danpure and Dawn Milliner began the meeting with introductions and background presentations on the molecular, genetic, and clinical features of the primary hyperoxalurias (PHs).

Background

Mutations in the *AGXT* gene (which encodes alanine-glyoxylate aminotransferase [AGT]), a peroxisomal enzyme, lead to type I PH, and mutations in the *GRHPR* gene (which encodes glyoxylate reductase [GR], and hydroxypyruvate reductase [HPR]) lead to type II PH. In addition, some patients have unclassified PH.

Dr. Milliner noted that most clinicians have limited experience with these rare, hereditary disorders, and this can lead to errors in diagnosis and management. Furthermore, because the diseases are rare, disease expression has not been well defined, progress defining the pathophysiology is slow, and researchers have had little opportunity to critically evaluate treatment interventions.

Dr. Steven Scheinman described other hereditary diseases that lead to calcium oxalate stone formation, including Dent's disease (associated with hypercalciuria), hereditary hypomagnesemia with hypercalciuria, and hereditary hypophosphatemia with hypercalciuria and rickets. Dent's disease is caused by mutations in the CLCN5 (chloride channel 5) gene.

Dr. Milliner then defined terms for the subsequent discussion:

- Hyperoxaluria—urine oxalate excretion rate > 0.5 mmol/1.73 m^2/24 hrs
- Oxalosis—deposition of calcium oxalate in renal and non-renal tissues
- Primary hyperoxaluria, type I—mutation of *AGXT* gene resulting in deficiency of hepatic AGT and hyperoxaluria
- Primary hyperoxaluria, type II—mutation of *GRHPR* gene resulting in deficiency of hepatic GR, HPR, and hyperoxaluria
- Primary hyperoxaluria, Undetermined Cause—persistent, marked hyperoxaluria without an identifiable secondary cause and not due to deficiency of hepatic AGT or GR/HPR

- Secondary hyperoxaluria—hyperoxaluria due to enteric oxalate hyperabsorption, excessive intake of oxalate or its precursors, pyridoxine deficiency, or other identifiable cause

Clinical and Research Goals for a Registry

Dr. Craig Langman opened this session by pointing out that a registry would allow discovery of patterns, associations, and changes that will improve clinical decisions and test diagnostic and therapeutic strategies. His points were echoed by Dr. Bernd Hoppe, who also noted that the registry would allow estimation of the prevalence and incidence of the disease and provide readily available information for use by clinicians and biomedical researchers. Both speakers suggested that the registry be used to disseminate information to the medical community, providing tutorials on symptoms, forms, diagnosis, and treatments.

Dr. Gill Rumsby discussed the importance of a mutation database, which would permit structural and functional analysis of the proteins and identification of sequence polymorphisms that have no phenotypic effect, perhaps leading, eventually, to prediction of the effects of newly discovered mutations and mapping of modifier loci. She then explained that detailed data on disease presentation, outcome, enzymatic activity, and other phenotypic measures would be needed to allow the mutation database to be used for genotype-phenotype correlations.

Finally, Mr. Brett Rosen from the Oxalosis and Hyperoxaluria Foundation observed that a database would unify international research efforts and centralize information, allowing the tracking of larger numbers of patients than are currently accessible to researchers.

Existing PH Databases

In this session, Dr. Neville Jamieson described the European registry of liver transplantation for PH, which was launched in 1990. Data from approximately 107 patients (84 of whom are current) are updated every two years using a detailed survey questionnaire that is completed by the treating physician. One of the major conclusions from analyzing the data is that there are clear correlations between length of dialysis before transplant and transplant outcome. However, this effort is unfunded and the voluntary reporting requirements are burdensome.

Dr. Jon Scheinman has analyzed existing large U.S. databases, including the U.S. Renal Data System (USRDS), the UNOS (United Network for Organ Sharing) transplant database, and the NAPRTCS (North American Pediatric Renal Transplant Cooperative Study) database. He has found that PH patients' survival improves with either a liver/kidney dual transplant or with a kidney-only transplant. Initially, survival is actually better with a kidney-only transplant, although that changes over time.

Mr. Berkeley Keck of UNOS described the characteristics of that network's OPTN (organ procurement and transplant network) database. The database contains information on approximately 142 pediatric and 213 adult liver and/or kidney transplant patients with PH.

Dr. Gill Rumsby discussed the PH mutation data that she will be contributing to the Human Genome Organization (HUGO) mutation database. The database will include information on silent/pathogenic mutations, source, context, mutation name and identifier. The goal is to include genotype-phenotype information, where possible, as well as data on compound heterozygotes.

Finally, Dr. Bernd Hoppe reviewed his U.S. survey on PH that was carried out several years ago. In that survey, data were collected on 102 patients, approximately 30 percent of whom were first diagnosed when they developed end-stage renal disease. Dr. Hoppe noted that his findings contrast with those of Dr. Scheinman, because they show that kidney-only transplant patients had significantly worse outcomes than liver and kidney patients, even though the dual organ transplants were associated with a high initial mortality rate.

Other Disease Registries

Dr. Neal Weinreb described Gaucher's disease and the registry that has been established by Genzyme. This registry is maintained by approximately 10 full-time employees, according to Neal Mantick of Genzyme. Advisers representing the biomedical community meet regularly to provide guidance to Genzyme and coordinate publications on registry data. Over 2,600 subjects are now included, and subregistries are used to collect extensive data from a subset of these individuals on issues such as quality of life, pregnancy. Dr. Weinreb also noted that Genzyme requires researchers to clear publications on registry data with the company.

Dr. Gregory Pastores spoke about the new Fabry's Disease registry being formed by Genzyme and discussed the goals of this database.

Finally, Dr. Vicky Whittemore described the Genetic Alliance's project to assist lay advocacy groups in setting up patient registries and her specific experience working with the Tuberous Sclerosis Alliance registry.

Draft Mission Statement for the Hereditary Calcium Oxalate Stone Disease Registry

The registry will contain information about patients with hereditary calcium oxalate stone disease caused by defects in oxalate metabolism, that is, primary hyperoxaluria (PH) or by Dent's disease, a specific defect of epithelial chloride channels.

The overall goal of the registry is to benefit patients and their families through improved diagnostics, treatments, and quality of life enhancements. The registry will achieve this aim in several ways. The use of data in the registry will make it possible to develop consensus guidelines for evidence-based management and to establish cohorts of patients for clinical trials. Educational activities will promote an understanding of disease development in the biomedical and patient communities and provide resources for evaluation, diagnosis, and management. Finally, data and materials collected through the registry will improve our understanding of the etiology and pathophysiology of diseases and will generate hypotheses for additional new research. Data in the registry will be generally available to the biomedical community, although a Scientific Review Board that will be responsible for reviewing all requests.

Specific Objectives

- Establish prevalence of primary hyperoxaluria (PH1, PH2, and atypical PH) and Dent's disease
- Establish characteristics of disease development over time, and identify prognostic markers
- Characterize non-PH1 and non-PH2 diseases
- Identify any correlations between genotype and phenotype by collecting data on mutations and polymorphisms in relation to biochemical and clinical data, including that obtained from longitudinal studies, in the same patients.
- Develop consensus standard methods for patient evaluation, including reference laboratories for clinical testing, as well as common protocols and reporting procedures.
- Develop model IRB application language for investigators applying to use registry data
- Establish well-defined patient cohorts for each of the included diseases
- Determine outcome and timing of clinical interventions

- Ensure high-quality data entry, using only physician-entered data, standardized units, cross checking of diagnosis with laboratory results, and providing the source of clinical laboratory data and normal range of that laboratory for each measure

- Further specific objectives may be added in the future in the light of new discoveries and the needs of the clinical, scientific and patient communities.

Access Guidelines

Data in the registry will be generally available to the biomedical community, using a registration process to review the requests for access. A tiered system will be implemented, allowing access only to the relevant subsets of data that are appropriate for the request. A Scientific Review Board will review all requests for access, and determine the scope of data that will be made available.

Detailed access guidelines will be developed based on those of other government and non-profit institution patient registries. In addition, standardized data sets will be made publicly available for general analysis. Patients will be allowed to view their own data and to withdraw from the registry at any time. Confidentiality of patient information will be strictly maintained. Names, initials, or other information that would permit identification of a specific patient will not be released. Rather, patients will be identified by a code number only.