Establishing a Longitudinal US Adrenal Insufficiency Cohort

Elizabeth A. Regan MD, PhD, Katherine E. Lowe BS, Madeleine Brown
National Jewish Health, Denver, Colorado USA

Background
Problem 1: No large US-based longitudinal cohort exists
The United States lacks a broad, longitudinal research cohort in adrenal insufficiency (AI) and has no data on disease prevalence or effectiveness of treatments. The US population, while strongly influenced by European immigration, may be quite different in disease expression from published European AI cohorts given the diverse African-American, Asian, Hispanic and other populations.

Problem 2: Multiple disease pathways need investigation
Adrenal Insufficiency is a final common pathway for a wide range of pathogenic mechanisms including: failure of the adrenal gland (Primary AI), central failure of hypothalamic or pituitary function (Secondary AI) and Congenital Adrenal Hyperplasia (CAH). Common patient issues may exist across these groups (or differ) – including inadequate hormone replacement regimens, with both persistent insufficiency symptoms and cortisol excess, persistent deficits in quality of life, ongoing risk of adrenal crises and potential excess mortality.

Problem 3: Rare diseases
Primary AI is a rare disease (presumably less than 100,000 individuals) and standard population sampling methods are not feasible. Local centers may recruit cohorts but these may be biased by unique diagnostic or treatment patterns as well as population structures influencing genetics. A national cohort offers information about overall treatment patterns, adequacy of current treatments and may provide novel information about the extent of disease in different racial and ethnic groups.

Problem 4: Natural History and Disease Progression
The various types of AI are often diagnosed as a dichotomous state (yes/no). However, evolving genetic and population data would suggest that autoimmune attack on adrenals or pituitary may occur over years and variable expressivity of genetic defects may lead to various populations who are at risk. Non-classic CAH may also produce a spectrum of disease severity. Little is known about function, quality of life or survival in these groups.

Methods
1. Cohort Development
Subjects will be recruited in the following categories using patient advocacy groups, social media, physician communications, direct advertising and word of mouth.

A). Adrenal Insufficiency: Primary, Secondary, Indeterminate, Congenital Adrenal Hyperplasia (CAH), Familial Glucocorticoid Deficiency (FGD)
B). At Risk: Autoimmune Disease, Oral Glucocorticoid Therapy, Family History of Adrenal Insufficiency
C). Control Subjects: age and gender similar (up to 4 per AI subject)

2. Procedures
   i. Online interface and subject initiation through the National Adrenal Diseases Foundation (NADF)
   ii. Data Storage through National Jewish Health
   iii. Data Collection Instruments (RedCap)
   a) Enrollment and Group Assignment
   b) Consent
   c) AI Diagnosis
   d) SF-36/ Adrenal Specific QoL
   e) Symptoms survey
   f) Medical history and medications
   g) Longitudinal – Brief Survey
   h) Longitudinal – Annual Survey

Results/ Conclusions
1. Ready to Start Enrollment this Summer
2. IRB submission Awaiting Only Final Review of Data Collection Forms
3. New Research Consortium for this Project Desired
Why?
A. To provide broad, long term scientific and clinical engagement
B. Inform AI patients of the opportunity to enroll in the project
C. Revise data collection instruments as needed
D. Utilize data as it accumulates
E. Define additional research aims
F. Provide researchers with patients for upcoming research protocols
Who?
Interested clinicians and researchers
Pharmaceutical groups
How?
Sign up today for further email updates and information

Future Directions for Adrenal Insufficiency
Treatment and Prevention of New Disease
1. Improved symptom control
2. Reduce deaths from Adrenal Crisis
3. Disease modifying treatments
4. Curative treatments
5. Enzyme replacement
6. Tissue engineering

Natural History of Disease

<table>
<thead>
<tr>
<th>Genetic or Environmental Risk Factors</th>
<th>Pathogenic Mechanisms Initiated</th>
<th>Subclinical Disease</th>
<th>Overt Disease</th>
<th>Late Stage and Death</th>
</tr>
</thead>
</table>

Study Groups
Adrenal Insufficiency
Primary – low 11 am cortisol with high ACTH and/or abnormal stimulation test
Secondary – low 11 am cortisol with low or normal ACTH and/or abnormal stimulation test
Congenital Adrenal Hyperplasia
Patient report of physician diagnosis – primary/secondary
Autoimmune Diseases
Patient report of autoimmune disease, chronic steroid use, family history of adrenal disease
Supplemented with personal medical records
At Risk
Family History/CAH
Males and females without autoimmune disease or adrenal insufficiency or steroid use
Stated Use
Age 18 and older

Congenital Adrenal Hyperplasia
- Patient report of genetic cause of AI, androgen excess, identification in early childhood or by newborn screening, enzyme defect/deficiency
- Compare steroid use alone (e.g., asthma) to steroid use associated with autoimmune diseases

Results/Conclusions
- Treatment and Prevention of New Disease
  1. Improved symptom control
  2. Reduce deaths from Adrenal Crisis
  3. Disease modifying treatments
  4. Curative treatments
  5. Enzyme replacement
  6. Tissue engineering

Future Directions for Adrenal Insufficiency
- Treatment and Prevention of New Disease
  1. Improved symptom control
  2. Reduce deaths from Adrenal Crisis
  3. Disease modifying treatments
  4. Curative treatments
  5. Enzyme replacement
  6. Tissue engineering