Hereditary dysautonomias: current knowledge and collaborations for the future
Introduction

There is increasing awareness that autonomic dysfunction, or dysautonomias, may be caused by various genetic perturbations. The hereditary dysautonomias (H-Dys) are a heterogeneous group of disorders. The better known dysautonomias are caused by genetic mutations directly or indirectly affecting catecholamine synthesis or metabolism. Several gene mutations have been identified which influence development and survival of autonomic neurons and produce variable but debilitating symptoms. Additional genetic and environmental factors affect disease severity. Although laboratory and clinical advancements have led to improved care for patients and their families, many hurdles remain. On October 3rd and 4th, 2002, in Rockville Maryland, the National Institute of Neurological Disorders and Stroke (NINDS), and the Office of Rare Diseases (ORD), National Institutes of Health (NIH), sponsored a landmark workshop on H-Dys, attended by numerous basic and clinical scientists, NIH representatives, members of advocacy groups and caregivers.

The workshop consisted of three excellent sessions, namely: (i) “Familial Dysautonomia (FD) – Genetics and Other Factors”; (ii) “Inherited Dysautonomias: Familial Dysautonomia and Beyond”; and (iii) “Lessons from Other Dysautonomias: An Overview”. A comprehensive list of speakers is outlined on Table 1. This first NIH sponsored H-Dys workshop was instrumental in promoting interactions between scientists and clinical investigators. It also allowed attendees to have an opportunity to meet each other, understand the similarities between the various forms of dysautonomia, and experience the unique perspective offered by patients and their families. Future advances in H-Dys research will depend on a novel multi-system approach by investigators from different medical disciplines, and it is hoped that towards a common goal, novel “bench-to-bedside” therapeutics will be developed to improve the lives of, or even cure, patients suffering from dysautonomic syndromes.

Abstract

The hereditary dysautonomias (H-Dys) are a large group of disorders that affect the autonomic nervous system. Research in the field of H-Dys is very challenging, because the disorders involve interdisciplinary, integrative, and “mind-body” connections. Recently, medical scientists, NIH/NINDS representatives, and several patient support groups gathered for the first time in order to discuss recent findings and future directions in the H-Dys field. The H-Dys workshop was instrumental in promoting interactions between basic science and clinical investigators. It also allowed attendees to have an opportunity to meet each other, discuss the workshop in more detail, summarizes the conclusions, and outlines recommendations for future directions in the H-Dys field.

Familial dysautonomia (FD)

Neuropathology and pathophysiology of FD

Riley et al. (1949) first reported 5 children of Ashkenazi Jewish descent, with central autonomic dysfunctions and defective lacrimation. Since that original observation more than 500 patients with familial dysautonomia (FD; Riley-Day syndrome) have been diagnosed [9,10]. Although FD has a variable phenotype at both the clinical and molecular level, all patients exhibit lack of overt emotional tears, absence of lingual fungiform papillae, decreased deep tendon reflexes, and loss of axon flare following intradermal histamine injection. Patients with FD exhibit sensory dysfunction as well as peripheral and central autonomic dysfunction. Sensory dysfunction includes diminished perception of pain and abnormal temperature appreciation. The autonomic dysfunction is manifested as hypotonia, excessive sweating and salivation, skin blotching, transient severe arterial hypertension, and other peripheral sympathetic deficits [9,10]. Patients with FD are highly susceptible to physical or emotional stress which can lead to “dysautonomic crisis.” A crisis is associated with a constellation of symptoms that are consistent with central sympathetic activation. In addition to tachycardia, hypertension, increased sweating and hyper-salivation, there is irritability, withdrawal, anxiety, and occasional self-mutilation [9,10]. Although early speculations suggested that the disease was caused by a dysfunction in neurotrans-