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Review article

Respiratory care in familial dysautonomia: Systematic review and expert consensus recommendations

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ABSTRACT

Background: Familial dysautonomia (Riley-Day syndrome, hereditary sensory autonomic neuropathy type-III) is a rare genetic disease caused by impaired development of sensory and afferent autonomic nerves. As a consequence, patients develop neurogenic dysphagia with frequent aspiration, chronic lung disease, and chemoreflex failure leading to severe sleep disordered breathing. The purpose of these guidelines is to provide recommendations for the diagnosis and treatment of respiratory disorders in familial dysautonomia.

Methods: We performed a systematic review to summarize the evidence related to our questions. When evidence was not sufficient, we used data from the New York University Familial Dysautonomia Patient Registry, a database containing ongoing prospective comprehensive clinical data from 670 cases. The evidence was summarized and discussed by a multidisciplinary panel of experts. Evidence-based and expert recommendations were then formulated, written, and graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

Results: Recommendations were formulated for or against specific diagnostic tests and clinical interventions. Diagnostic tests reviewed included radiological evaluation, dysphagia evaluation, gastroesophageal evaluation, bronchoscopy and bronchoalveolar lavage, pulmonary function tests, laryngoscopy and polysomnography. Clinical interventions and therapies reviewed included prevention and management of aspiration, airway mucus clearance and chest physical therapy, viral respiratory infections, precautions during high altitude or air-flight travel, non-invasive ventilation during sleep, antibiotic therapy, steroid therapy, oxygen therapy, gastrostomy tube placement, Nissen fundoplication surgery, scoliosis surgery, tracheostomy and lung lobectomy.

Conclusions: Expert recommendations for the diagnosis and management of respiratory disease in patients with familial dysautonomia are provided. Frequent reassessment and updating will be needed.

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1. Introduction

Familial dysautonomia (FD, Riley-Day syndrome, hereditary sensory and autonomic neuropathy type III, OMIM 223900) is a rare autosomal recessive disease, present at birth, first described in 1949 in children of Central European (Ashkenazi) Jewish ancestry [1]. The disorder is caused by a founder mutation in the IkB kinase-associated protein gene (*IKBKAP*) [2]. This produces a deficiency of the protein IKAP (ELP-1), causing impaired development of sensory and afferent autonomic nerves [3].

Hallmarks of FD include impaired pain and temperature sensation, reduced basal tear production [4], absent deep tendon reflexes, optic neuropathy [5], gait ataxia [6], blood pressure instability owing to afferent baroreflex failure [7–9], neurogenic dysphagia [10], chemoreflex failure [11,12], sleep-disordered breathing [13–15], and chronic lung disease [16], all which contribute to morbidity and mortality [3,13]. Respiratory disease remains one of the leading causes of death in patients with FD [3].

Due to the rarity of the disease, the management of its respiratory aspects has been based on empirical decisions without controlled clinical trials [17]. Until now, there were no guidelines for the management of respiratory disease in children or adults with FD. The purpose of this document is to: (a) describe the multiple aspects of airway disease in FD; (b) provide a practical standardized framework for the assessment and management of respiratory disease in this fragile patient population; and (c) identify areas for future research. These recommendations are for both children and adults, with differences in the groups acknowledged when necessary.

2. Methods

In January 2016, a task force met to discuss and develop expert-based consensus recommendations. The members of the task force were selected based on their experience with patients with FD and their broad-based expertise to cover multiple aspects of the disease. A literature review committee (J.A.P, C.L.S., E.P.B., L.N.K.) performed a literature search using PubMed, EMBASE, and *Google Scholar* including articles published from 1949 to 2017. Search terms included combinations of “familial dysautonomia”, “Riley-Day syndrome”, “hereditary sensory and autonomic neuropathy type III”, and “respiratory”, “pneumonia”, “sleep”, “fundoplication”, “ventilation”, “apnea”, “oxygen”, “infections”, “chest”, “dysphagia”, “therapy”. Only English-language publications were considered. This initial search yielded sixty-one articles. Three authors (C.L.S., J.A.P. and L.N.K.) independently screened all titles and abstracts generated by the search. The full texts of screened articles were independently assessed for inclusion. Original research that reported data relevant to the assessment or management of respiratory disorders in patients with FD was included. To identify additional studies, reference lists of included articles and review papers were screened, and relevant journals and proceedings of key scientific meetings were hand searched. Consensus was required for final exclusion of screened articles and disagreements were resolved through involvement of a fourth author (H.K.). Abstracted data included: study methodology (design, number of subjects), and outcomes. Due to the rarity of the disease, case reports were included in the final list of included articles.

Twenty-five full text articles were included in the final search with emphasis given to articles published after 1990. This information was subsequently presented to the full task force, after which there was discussion and drafting of the recommendations. The task force acknowledged that certain existing principles on diagnosis and management of respiratory disease in other disorders would be applicable to FD. Thus, the expert panel reviewed and referenced the additional body of literature related to aspiration-related diseases and non-cystic fibrosis bronchiectasis when appropriate.

The level of evidence and strength of the recommendation was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [18]. The GRADE system classifies recommendations as *strong* (grade 1) or *weak* (grade 2), either for or against a specific recommendation [18]. Factors determining the strength of recommendation include a balance between desirable and undesirable effects, quality of evidence, the values and preferences of the experts, and the costs of the intervention. The task force acknowledged i) the potential limitations of making recommendations in the presence of low-quality evidence, and ii) the fact that the strength of the recommendation was defined taking into consideration the paucity of research data available related to this rare genetic disease.

A strong recommendation is worded as “we recommend” and a weak recommendation is worded as “we suggest.” The quality of evidence is an estimate of the certainty of the estimated treatment effect. An (A) rating conveys that the data were derived from multiple randomized clinical trials or meta-analyses; a (B) rating indicates that data were derived from one randomized clinical trial or high-quality observational studies; a (C) rating indicates that data were derived from observational studies; and a (D) rating indicates that recommendations are based on low-quality observational studies, case reports, or expert clinical experience.

Because of the limited number of published reports in patients with FD, prospective clinical data from the NYU Familial Dysautonomia Patient Registry was reviewed to address knowledge gaps. The NYU FD Registry is an ongoing, prospective registry of patient with FD that tracks the natural history of the disease with standardized clinical data collected annually. The Registry started in 1970 and contains clinical and diagnostic data, including cause of death, on 670 patients at the time of writing this document. Patients are followed closely and seen at least once a year.

A writing committee prepared the initial draft and then incorporated comments from all remaining coauthors. While recognizing the small number of published studies on the respiratory aspects of FD, the task force agreed to develop practical expert consensus guidelines that reflected the current state of the art. It is acknowledged that in the vast majority of cases, recommendations are based on the consensus of non-systematic clinical observations [i.e., quality of evidence (D)], rather than the results of randomized clinical trials. These guidelines are intended to assist health care providers in clinical decision making by describing generally acceptable approaches to the diagnosis and management of respiratory disorders in patients with FD.

3. Epidemiology of respiratory disorders in FD

Respiratory abnormalities are a prominent feature of FD. Patients have varying degrees of upper airway obstruction (83%), lower airway disease (85%), and restrictive lung disease (94%) (NYU FD Registry, 2016). Approximately 85% of adults and 91% of pediatric patients [15] have some degree of sleep-disordered breathing which, when untreated, is a risk factor for sudden unexpected death during sleep (SUDS), a leading cause of death in FD [13].

Neurogenic dysphagia occurs in all patients and is usually the presenting neonatal feature [3,19]. Most patients with FD will develop chronic lung disease, due, in large part, to recurrent aspiration. Currently, 85% of patients have a gastrostomy tube placed for hydration and feeding to reduce the overall risk of aspiration. To prevent gastroesophageal reflux, another potential source of aspiration, most patients had a Nissen fundoplication at the time of gastrostomy [20,21](NYU FD Registry, 2016). Despite these procedures, recurrent lower airway infections are common with an average of 10 pneumonias per lifetime (FD Registry, 2016). Computerized tomographic (CT) imaging of the chest shows bronchial wall thickening in 94% and bronchiectasis in 26% of patients [22]. Chronic hypoxemia ($PaO_2 < 80$ mmHg) is present in 40% of patients and 16% have daytime hypercapnia ($PaCO_2 \geq 50$ mmHg) (NYU FD Registry, 2016).