



Original Article

Attention deficit hyperactivity disorder symptoms in patients with cystic fibrosis

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Abstract

Background: Cystic fibrosis (CF) is a chronic life-threatening disease. In patients who suffer from chronic disease, Attention Deficit Hyperactivity Disorder (ADHD) is associated with functional impairment that can affect adherence to treatment and consequently influence prognosis.

Methods: CF patients filled in the ADHD Rating Scale (ADHD-RS) adapted to the DSM5 and were assessed on a continuous performance task (MOXO-CPT), a standardized-computerized test designed to evaluate several domains of attention.

Results: Of the 175 patients (99 males), 18% presented ADHD symptoms, according to ADHD-RS; 16% in the younger group (<18 years), and 18.9% in the adult group. The male to female ratio was 3:1 in children and 1:1 in adults.

Conclusions: The occurrence of ADHD symptoms in patients with CF is substantially higher than in the general population and should be recognized as a co-morbidity of CF. As ADHD can impair adherence to therapy, further research is needed to investigate the effect of ADHD therapy on adherence.

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Keywords: Cystic fibrosis; ADHD; Adherence; Chronic illness; Inflammatory disease

1. Introduction

Cystic fibrosis (CF) is the most common inherited disease, with a carrier frequency of 1:25 in the Caucasian population. Recurrent respiratory tract infection and chronic airway inflammation are the hallmark of CF lung disease [1], and patients must dedicate time and energy to manage all manifestations of their

illness. Treatment includes daily respiratory physiotherapy, 3–6 inhalations per day, multiple oral medications, and intermittent intravenous antibiotic therapy. During exacerbations patients usually visit the CF center more often, require more intensive treatment and sometimes hospitalization is necessary, which disrupts the patient's and their families' daily life routine.

Intensive treatment is important for the prognosis of CF patients [2]. Treating a child with CF is a great burden for parents and family, especially during adolescence [3]. This is extremely important since family function and intra-familial relationships have a direct influence on treatment success [4]. Moreover, patients who suffer from chronic disease are more

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likely to have psychiatric/behavioral comorbidities [5–6]. Much effort has been made to improve the quality of primary care for patients with CF, but not enough is known of the association between this chronic health condition and cognitive performance factors such as attention deficit [6].

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder [7], with an estimated prevalence worldwide of 5%–7% [8]. It is becoming clear that at least in some patients, inflammatory responses in the brain as a result of different postnatal environmental and genetics risk factors may play a significant role in human behavior in general and in ADHD in particular [9,10]. Thus, although the etiology of ADHD is neurobiological, previous studies have reported increased inflammatory markers in ADHD, suggesting a possible association with chronic inflammatory illnesses [11].

When patients who suffer from ADHD have to deal with a complicated and life threatening disease such as CF, it can affect adherence to treatment and consequently prognosis [12]. Nevertheless, few studies have investigated the influence of ADHD on treatment and prognosis in patients with CF [13]. We hypothesized that ADHD symptoms could cause deterioration of the root illness as a result of treatment adherence failures (e.g., forgetting, executive functioning deficits, difficulty organizing and following a schedule). The goal of this study was to determine the rate of ADHD symptoms in children and adults with CF and test for associations with medical variables.

2. Patients and methods

2.1. Participants' demographics

One hundred and seventy-five patients, 99 males (56.6%) and 76 females (43.4%), from four CF centers (3 in Israel and 1 in Spain) participated in this study. The median age of the participants was 18 years, with an average of 20.85 (SD 12.02). The forced expiratory volume in one second (FEV₁)% predicted for 147 patients (28 with missing data) was 77.7% (SD 22.25) and the mean body mass index (BMI) percentile was 48.7 (SD 28.3). Out of 170 patients (5 cases of missing data), 83 (47.4%) were chronically infected with *Pseudomonas*. Patients with CF \geq 6 years old were included in this study. Participants were recruited at three CF centers in Israel (Hadassah-Hebrew University Medical Center, Jerusalem, Graub CF Center of the Schneider Children's Medical Center, Petach-Tikva, and the Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa), and one CF Center in Spain (Hospital Universitari Vall d' Hebron, Barcelona). Informed consent was obtained from all participants above 18 years old and from parents of participants under 18. All protocols were approved by each hospital's Institutional Review Board (Helsinki Committee). Patients who had previously been diagnosed with ADHD (fulfilling ADHD-RS criteria) were included in the *positive* group. None of these patients were being treated with stimulants or any other ADHD-related medications on a regular basis, for reasons that are beyond the scope of this study.

Each participant included in the study was evaluated as follows:

1. ADHD symptoms were assessed using a validated ADHD Rating Scale (ADHD-RS) [14,15] that has been translated and used in Israel as reported in previous studies [16–18] for children [14] and adults [15].

This 18-item ADHD Rating Scale, incorporates changes to the Diagnostic and Statistical Manual of Mental Disorders [7], and is comprised of two sub-scales that assess inattention (nine items) and hyperactivity/impulsivity (nine items) symptoms. The questionnaires were completed as a function of the age group: for children aged 6 to 11, both parents were asked to fill out the ADHD-RS [14]; with both parents' responses needing to be elevated for the child to be counted as ADHD positive; for adolescents, \geq 12 to 17, a parent form and an individual-patient form was used [14,15], both questionnaires needed to be ADHD positive; for adults \geq 18 years old, an independent form was completed [15].

2. Participants then took a continuous performance task (CPT) in a ventilated room under special infection-control procedures as required. The MOXO-CPT [16] is designed to diagnose ADHD related symptoms. This CPT (Neuro-Tech Solutions Ltd) is a standardized, language free, computerized test, which is internationally accepted and validated. It is made up of a combination of tasks based on an algorithm designed to test several domains of attention. The participants are required to sustain their attention over a continuous stream of cartoon stimuli and to respond to a pre-specified target, but it also includes visual and auditory stimuli serving as measurable distractors [17]. The MOXO-CPT has norms for a large age range (children, adolescents and adults). In previous studies the MOXO-CPT consistently distinguished between children, adolescents and adults with ADHD and their unaffected peers, in that ADHD patients performed less well than controls in all study indices [16–18].

Demographic and clinical data was extracted from patient files. We analyzed characteristics of CF that are known to be associated with the severity of the disease including pulmonary function testing, measured by FEV₁ percent predicted, nutritional status represented by the BMI percentile adjusted to age and gender, and the presence of chronic *Pseudomonas aeruginosa* colonization in the sputum [19], defined by Leeds criteria: airway samples which are *Pseudomonas* positive in $>$ 50% of the explored months [20]. The clinical data were analyzed and comparisons were conducted across patients.

2.2. Data analysis

Analysis of the ADHD-RS as defined in DSM 5: in order to fulfill the diagnostic criteria for ADHD, children needed to exhibit at least 6 symptoms compatible with an ADHD pattern of inattention and/or hyperactivity-impulsivity. In patients \geq 18 years old, five of the symptoms were considered sufficient

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