Topical Review: Eosinophilic Esophagitis in Children: Implications for Health-Related Quality of Life and Potential Avenues for Future Research

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Received December 18, 2014; revisions received March 12, 2015; accepted March 12, 2015

Abstract

Objective To characterize the health-related quality of life (HRQoL) of children with eosinophilic esophagitis (EoE) as well as generate novel hypotheses for future research in this pediatric population. Method A literature review was completed using PubMed and the keywords below. Results Research has shown that for children with EoE and their parents, symptom experiences and recommended treatments can have a negative impact on HRQoL. However, studies have yet to adequately address mechanisms that may help explain why this is. Areas of interest include sleep quality and disturbances, the experience of pain, and the presence of internalizing symptoms, all of which have the potential to uniquely and synergistically impact HRQoL. Conclusion With greater understanding of the associations among sleep, pain, internalizing symptoms, and HRQoL in children with EoE may come enhanced therapies that substantially improve the quality of their health care.

Key words: Eosinophilic esophagitis; health-related quality of life; pain; pediatric; sleep.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease marked clinically by symptoms of upper gastrointestinal distress and by pathologic findings of increased eosinophils in the esophagus (Dellon et al., 2013). EoE is predominantly observed in pediatric populations, with initial diagnoses made in children as young as 6 months of age (Khan et al., 2003). Specifically as it relates to children, most EoE symptoms are triggered by allergic hypersensitivity to foods, and can include recurrent symptoms of esophageal, chest, and epigastric pain, as well as vomiting, dysphagia, and food bolus impaction that can lead to feeding aversion (Iwanczak et al., 2011; Liacouras et al., 2011). Symptom experiences, diagnostic procedures, and recommended treatments related to the disease can have a tremendous impact on the health-related quality of life (HRQoL) of many pediatric patients as well as the quality of life and psychological well-being of their families (Cortina et al., 2010; Franciosi et al., 2012; Klinnert, 2009). However, because EoE in children has only recently been recognized and defined as a clinical syndrome, much about the impact of this disorder on HRQoL remains to be characterized. Furthermore, systematic research is lacking regarding the psychological effects of EoE on children and the impact of the disease on other important factors such as sleep patterns and the experience of pain. Despite the current lack of research regarding EoE in children, some hypotheses can be gleaned by
drawing upon existing research regarding HRQoL among children with comparable chronic illnesses. For instance, similar to children with irritable bowel syndrome and juvenile rheumatoid arthritis, children with EoE may experience poor sleep, enhanced pain, and mood disturbances as identified through behavioral health interviews and self-report questionnaires (Harris, Menard-Katcher, Atkins, Furuta, & Klinnert, 2013; Ingerski et al., 2010). These symptom experiences, in turn, all directly and negatively affect HRQoL.

**EoE Epidemiology, Diagnosis, Clinical Symptoms, and Treatments**

The overall prevalence of pediatric EoE in the United States has been estimated to be approximately 10–50/100,000 children (Noel, Putnam, & Rothenberg, 2004). However, there is a sense among the pediatric gastroenterology community that the incidence of EoE is increasing above and beyond the recent diagnostic shift that has facilitated disease recognition (Cherian, Smith, & Forbes 2006). EoE presents most often in Caucasian males, with peaks in diagnosis around ages 1, 7, and 11 years (Assa’ad et al., 2007). More specifically, it has been reported in the literature that approximately 75% of the diagnosed EoE cases are male, while nearly 90% report their racial background as Caucasian (Assa’ad et al., 2007; Hommel et al., 2012; Noel et al., 2004; Spergel et al., 2011). Despite these initial reports, it should be noted that epidemiological studies addressing pediatric EoE prevalence across diverse populations of children are currently lacking. Therefore, one area for future research is to better estimate rates of EoE in children from ethnic/racial minority backgrounds.

EoE can be difficult to diagnose because symptoms often mimic those of other gastrointestinal diseases. Both pathologic and clinical symptoms must be considered for appropriate diagnosis. EoE is often recognized pathologically through endoscopy and biopsy demonstrating eosinophil-predominant inflammation of the esophagus exceeding 15 eosinophils/high-power field (eos/hpf) (Iwanczak et al., 2011). Endoscopy may also show longitudinal furrows (i.e., grooves), mucosal rings, whitish exudates (i.e., emitted fluids), nodules, and constriction (Iwanczak et al., 2011). Importantly, EoE must not be responsive to proton pump inhibitors in order to exclude differential diagnoses of proton pump inhibitor esophageal eosinophilia and gastroesophageal reflux disease (Dellon et al., 2013).

Clinically, EoE is characterized by feeding aversion, dysphagia, food impaction, vomiting and esophageal, chest, and/or abdominal pain (Liacouras et al., 2011). The presentation of specific EoE symptoms often varies by age. It has been reported that children aged 2–7 years most commonly present with vomiting, reflux, and malnutrition, whereas older children and teens tend to experience greater severity of epigastric and abdominal pain, dysphagia, and vomiting (Flood et al., 2008; Iwanczak et al., 2011; Noel et al., 2004). Disease progression and negative effects on the esophagus may result in increased risk of strictures, dysphagia, and impaction as patients become older (Schoepfer et al., 2013; Spergel et al., 2011).

The treatments for EoE primarily come in three forms, including dietary, pharmacologic, and endoscopic; all of which may be combined for maximum likelihood of disease remission (Dellon et al., 2013). Dietary therapy can include the strict use of amino acid-based formulas as well as targeted dietary eliminations based on results of extensive allergy testing. Eliminating the most likely food antigens can be quite effective, given the suspected antigen-mediated etiology of EoE. Topical corticosteroids, or swallowed inhaled steroid therapy, may also be prescribed to reduce the esophageal inflammation associated with the disease. These medications are occasionally mixed with a thick sweetener and then swallowed, which allows the steroid to coat the throat. Finally, on rare occasions, esophageal dilation may provide relief of dysphagia (Liacouras et al., 2011). EoE is a chronic disorder requiring ongoing therapy, but there is limited knowledge on the long-term efficacy of current treatments. EoE symptoms typically return, or increase in severity, when therapy is stopped (Blanchard, Wang, & Rothenberg, 2006).

**EoE and HRQoL**

HRQoL focuses more directly on the impact health status has on quality of life and life satisfaction, rather than measures of morbidity and mortality. HRQoL is a multidimensional concept that includes domains related to physical, psychological, and social functioning (Drotar, 2014). Children with chronic gastrointestinal diseases including EoE often experience negative changes in all of the functional domains that comprise HRQoL. Furthermore, the parents of these children also report decrements to their own quality of life and that of other family members such as brothers and sisters (Klinnert, 2009). Cortina and colleagues (2010) found that children with eosinophilic gastrointestinal disorders (EGIDs) (e.g., EoE) had significantly poorer HRQoL than healthy control children, as reported on the PedsQL. In another study examining HRQoL across different pediatric chronic illnesses, caregivers of children with EGID reported significantly lower HRQoL than children with cystic fibrosis, inflammatory bowel disease, epilepsy, Type 1 diabetes, and sickle cell disease (Ingerski et al., 2010).
The negative impact on HRQoL may be influenced by children experiencing persistent symptoms, following daily medical and/or dietary treatments, coping with the burden of elimination diets, and uncertainty about their future given the chronic nature of EoE. Klinnert and colleagues (2014) reported results of a longitudinal study indicating that for children with EoE, a greater number of symptoms at baseline were related to poorer HRQoL. Furthermore, as symptom severity decreased from baseline to the 6-month follow-up, HRQoL concomitantly improved. In addition to EoE disease symptoms, HRQoL can also be impacted by the treatment of the disease. Dietary restrictions and eliminations are often a key component of EoE treatment, which can affect eating habits and favorite foods. Eliminating favorite foods and dietary changes have the potential to affect HRQoL, given the emotional investment children can have in favorite foods and eating habits (Klinnert, 2009). Parents and caregivers may also experience resistance from children regarding the need for dietary changes. Unlike many children with food allergies, an immediate reaction to the offending food is not readily apparent to children with EoE, thereby making it difficult to understand the need to remove the food from their diet (Klinnert, 2009).

**HRQoL Knowledge Gaps and Areas for Future Research**

To date, no studies have specifically examined whether pain levels and sleep patterns may be related to HRQoL in children with EoE. This is concerning because it has been reported that up to 60% of children with EoE report recurrent epigastric and abdominal pain, while 28.3% also report chest pain (Pentiuk, Putnam, Collins, & Rothenberg, 2009). Importantly, the chronicity of these recurrent pain episodes has not been well-characterized to date for children with EoE. Therefore, the prevalence of chronic pain in this

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**Figure 1.** Conceptual model demonstrating how EoE symptoms and treatments can directly influence HRQoL, but also how HRQoL may come to be indirectly impacted by the effects of EoE symptoms and treatments through pain, sleep, and internalizing symptoms. EoE = eosinophilic esophagitis; HRQoL = health-related quality of life.
pediatric population remains largely unknown. Initial evidence has, however, indicated that younger children more readily report pain in the abdominal region, while adolescents often identify pain in the chest in addition to the abdomen (Liacouras, Spergel, & Gober, 2014). Because not every child with EoE will experience recurrent pain, longitudinal studies are needed to better identify which children are at greatest risk for developing a recurrent pain condition and why. Moreover, it has also been reported that 25–33% of children with EoE experience moderate to severe sleep difficulties (Flood et al., 2008; Straumann et al., 2012); however, the nature of these sleep difficulties has not been well-described in previous studies. Sleep is a multidimensional health factor that is affected by circadian rhythms as well as habits and behaviors, and disorders of sleep can have physiological and behavioral etiologies. The mechanisms (i.e., physiology, habits, behaviors) contributing to sleep difficulties in children with EoE have not been addressed, and further research is needed examining how and why sleep difficulties may come to negatively impact the HRQoL of these children.

The presence of pain, even when only mildly severe, can disturb sleep and decrease its quality through a number of pathways. For instance, persistent pain creates a heightened vigilance to signals of impending pain flares as well as creating cognitive and emotional changes that can make it difficult to fall asleep and stay asleep (Finan, Goodin, & Smith, 2013). In turn, poor sleep quality can lead to an increased sensitivity to pain, creating a vicious cycle that results in decreased HRQoL (Palermo, Fonareva, & Janosy, 2008). It may also be that younger children who regularly wake up at night are more likely to also awaken their parents and disrupt their sleep, which may further negatively impact parental quality of life. Further prospective research is needed to better characterize the nature of the sleep difficulties experienced by children with EoE, and consideration should be given to the effects of age and development on sleep as well as the associations of sleep with pain, other symptoms of EoE, and HRQoL.

When addressing the HRQoL of children with EoE, future research should also consider children’s psychological functioning and internalizing symptoms. Children with EGID, of which EoE is a subset, tend to have poorer psychological functioning, with greater internalizing symptomology and a higher degree of somatization than their healthy peers (Cortina et al., 2010). In fact, Cortina and colleagues (2010) documented almost half of the children with EGID displayed clinically significant levels of internalizing symptomology. Findings were further corroborated by Harris and colleagues (2013), whereby 69% of children with EoE experienced some form of problem suggestive of poor psychological functioning, ranging from social and school difficulties to depression and anxiety. Consideration for the psychological functioning and internalizing symptoms of children with EoE is important for two aspects particularly relevant to the focus of this topical review: (1) across multiple populations of children, both healthy and chronically ill, internalizing symptoms have been shown to significantly and negatively impact HRQoL (Stevanovic, 2013); and (2) internalizing symptoms appear to be strongly associated with sleep disturbances, pain, and HRQoL in children (Palermo & Kiska, 2005). Although a few studies have already examined various aspects of psychological functioning and internalizing symptoms in relation to the HRQoL of children with EoE, no study to date has simultaneously examined sleep, pain, internalizing symptoms, and HRQoL.

Finally, it will also be important for future researchers to consider the impact of aging and development on the HRQoL of children with EoE. Although this point has yet to be directly addressed in pediatric EoE populations, studies of healthy children have found that HRQoL tends to decrease during the transition from childhood to adolescence (Michel, Bisegger, Fuhr, & Abel, 2009). Therefore, it may be that the HRQoL of children with EoE is at even greater risk due to their chronic illness and developmental course. The most affected HRQoL domain might vary according to the age and development of children with EoE. For instance, physical HRQoL may initially be more affected in younger children due to the emergence of clinical symptoms, while psychological and social HRQoL becomes more negatively affected as children grow older owing to school absenteeism and altered peer relationships; empirical support for this hypothesis is currently lacking. Furthermore, aging and development likely impacts the presentation and progression of pain, sleep difficulties, and internalizing symptoms in children with EoE; however, this remains to be determined.

Conclusion

Figure 1 provides a simplified, working conceptual model describing both direct and indirect pathways by which the HRQoL of children with EoE and their parents may come to be affected. In the future, individuals who treat and research pediatric chronic inflammatory gastrointestinal diseases like EoE need to pay more attention to the role that important clinical factors, such as sleep, pain, and internalizing symptoms, play in the appreciation of HRQoL. Importantly, the National Institutes of Health Patient Reported Outcomes Measurement Information System initiative has developed freely available pediatric self-report and parent proxy item banks that can assist clinicians and
researchers with assessment of these clinical factors; http://www.nihpromis.org. Determining how current and future empirical findings addressing HRQoL in children with EoE can best be translated into improved clinical practice represents an important effort moving forward. For example, with greater understanding and recognition of the pain and sleep patterns of children with EoE may come enhanced therapies that augment the medical plan of care. Given the efficacy of cognitive-behavioral treatments for improving pediatric pain and sleep outcomes (Eccleston, Morley, Williams, Yorke, & Mastroyannopoulou, 2002; Sadeh, 2005), psychological services may perhaps become more commonly integrated into the pediatric gastroenterology clinics that provide much of the specialty care for children with EoE. By targeting pain management and the maintenance of adequate sleep, psychologists could help produce positive trends in patients’ HRQoL through decreased levels of internalizing symptoms like depression and anxiety.

Conflicts of interest: None declared.

References


