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Potential Role of Bordetella Pertussis in Celiac Disease

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Abstract We discuss the correlation between the incidence of acute clinical Bordetella pertussis infection and celiac disease in children < 2 years of age during the Swedish celiac disease epidemic of the 1980s and 1990s.

Keywords: *celiac disease, Bordetella pertussis, subclinical Bordetella pertussis colonization (SCBPC)*

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1. Introduction

Marked increases in celiac disease (CD) prevalence in recent decades have expanded investigation into potential environmental causes and underlying mechanisms of CD. A 2014 review examined the challenges to establishing a rodent model for CD, highlighting methods to overcome immunologic tolerance to oral gluten, including the use of bacterial adjuvants [1]. Bordetella pertussis toxin (BP_{TOX}) is one such adjuvant used in many animal models of human autoimmune and allergic disease [1,2,3], including CD-associated dermatitis herpetiformis, and intraperitoneal BP_{TOX}-mediated gluten sensitization reproduces CD markers [1]. Interestingly, animal modeling demonstrates that "nanogram quantities of PT [pertussis toxin, BP_{TOX}], when administered with a food protein, result in long–term sensitization to the antigen" in the small intestine [3].

Mindful of the adjuvanticity of BP_{TOX}, we note the concurrent decades-long rise in rates of CD [4] and Bordetella pertussis (BP) in the United States, the latter ascribed to multiple factors, including the inability of acellular pertussis (aP) vaccination to prevent subclinical BP colonization (SCBPC) [5]. Recent human data confirm nasopharyngeal SCBPC by polymerase chain reaction in 4.8% of asymptomatic children in a highly (99%) aP-vaccinated population [6]. Given the potential biologic effects of SCBPC, we compared the rates of acute BP and CD in children < 2 years of age during the Swedish CD epidemic of the 1980s and 1990s.

2. Discussion

Figure 1 presents the concurrence of acute BP (whooping cough) and CD during the Swedish CD epidemic, most notable for simultaneous and rapid declines associated with the reintroduction of pertussis vaccination after a 15 year national hiatus. Most Swedish children received whole cell BP vaccination from the 1950s to 1979, when it was suspended for efficacy and safety concerns [7]. While mean CD incidence subsequently increased, infant CD ascertainment was likely limited prior to the emergence of serum IgA-based screening tests in 1983-1984 [8]. Such blood-based screening rapidly gained acceptance with consideration in European practice guidelines by 1990 [8].

As seen in Figure 1, covariation between BP and infant CD is evident from 1986 to 2000, peaking together in 1994.

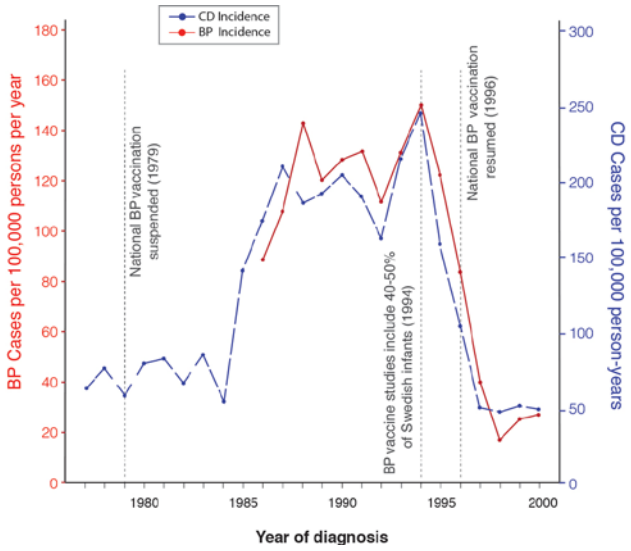

Figure 1. Concurrent Swedish Pertussis and Celiac Disease Epidemics, 1986-2000. The cessation of BP immunization in Sweden in 1979 preceded a rise in BP in the 1980s, persisting until acellular BP vaccination trials in 1993-1994 and broad implementation of vaccination in 1996 (red line) [7]. The incidence of CD in Swedish children < 2 years of age, based on data from Olsson et al. (dashed blue line) [9], closely tracks BP incidence in Sweden during this period.

The resurgence of BP prompted aP vaccination trials by 1993-1994, immunizing 40-50% of Swedish infants [7]. Abrupt proportionate decreases in BP and CD followed. In 1996, nation-wide aP vaccination resumed, reinforcing the drop in BP rates. Of the many Swedish childhood vaccination programs tracked from 1980-2000, the only disease for which vaccine coverage increased as infant CD declined in the 1990s, was BP [10].

Despite the association between acute BP and CD incidence, no association was found between aP vaccination and CD in the same child [10]. Since aP vaccination directly protects against acute BP but not against CD, acute BP must have covaried with another cause of CD. We propose that acute BP and SCBPC carry distinct disease risk profiles. As aP vaccination fails to prevent SCBPC in primates [5], and SCBPC persists in highly aP-vaccinated human populations [6], we propose that SCBPC covaried with acute BP and CD in Sweden, and is an unrecognized cause of CD. We further submit that reintroduction of aP vaccination in the 1990s reduced SCBPC indirectly, by decreasing ambient BP exposure and seeding of SCBPC. The role of nasopharyngeal SCBPC-mediated sensitization in CD animal models, and more broadly, in allergic and autoimmune human disease merits further investigation.

3. Conclusion

Given the covariation between BP and CD in Sweden, that BP and BP_{TOX} are potent adjuvants, that SCBPC secretes BP_{TOX} and is common in highly aP-vaccinated populations, that intraperitoneal BP_{TOX}-mediated gluten sensitization (without colocalization) reproduces CD markers, and that minute quantities of BP_{TOX} administered with otherwise non-imunogenic food protein induce long–term antigen sensitization, it is biologically plausible that SCBPC-mediated mucosal sensitization to colocalized gliadin is a major unrecognized cause of CD.

Statement of Competing Interests

Drs. Rubin and Glazer are employed by ILiAD Biotechnologies LLC, which is developing a vaccine for the prevention of Bordetella pertussis.

Abbreviations

BP_{TOX}: Bordetella pertussis toxin
aP: acellular pertussis
SCBPC: subclinical Bordetella pertussis colonization.

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