Autoimmunity Hypotheses for The National Children's Study

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Autoimmune diseases are common childhood disorders, collectively constituting more than 5% and possibly up to 10% of all pediatric illnesses. Autoimmune diseases are disorders in which the humoral and/or T lymphocyte arms of immune system attack self-tissues or self-antigens and they generally result in an inflammatory response; they are often characterized by the presence of autoantibodies (Cooper, GC et al, 2002). Autoimmune diseases may be limited to a specific organ (e.g., type I diabetes mellitus, thyroiditis, immune thrombocytopenia purpura), or they may be systemic, involving at least two, or often multiple organ system targets (e.g., systemic lupus erythematosus, systemic vasculitides). The precise number of autoimmune diseases in childhood that are classified under this group of diseases is not known, but one group places the number at more than 50 different disorders (www.aarda.org/directory.html). Some of the most common examples of autoimmune diseases present throughout childhood include (Nelson Textbook of Pediatrics, 16th ed, unless otherwise noted):

Thyroiditis (Graves' and Hashimoto's thyroiditis): incidence ~1% among school children; prevalence 630 cases/100,000 (Cooper et al, 2002)

Ulcerative colitis and Crohn's disease: ~20 new cases per 100,000 per year

Type I diabetes mellitus: > 14 new cases per 100,000 per year; prevalence 190 cases per 100,000 (Cooper GC et al, 2002)

Juvenile rheumatoid arthritis: ~14 new cases per 100,000 per year (Lawrence RC et al, 1999); prevalence 94 cases per 100,000 (Peterson et al, 1996)

Psoriasis: one third of all cases with onset in childhood

Celiac Sprue: 1/10,000 live births

Immune Thrombocytopenia Purpura (ITP): Prevalence 5.3 cases/100,000 children (Zeller B et al, 2000)

Vitiligo: prevalence 0.17 – 0.5% of childhood population

These disorders are not only common, and thought to be increasing in frequency due to novel environmental exposures, but they are also very often chronic conditions. As such, these disorders represent a disproportionate burden to our society and health care system, both in terms of health care dollars (Javitz HS et al, 2002), as well as the costs of morbidity from missed school and work, and ultimate costs of altered occupations, etc. They are often also associated with increased mortality (Jacobson DL et al, 1997). They are thus deserving of the study's attention, as a group of diseases that have high impact on child health.

The etiology of autoimmune diseases is thought to result from multiple genetic risk factors which are triggered by one or more environmental factors (Cooper GS et al, 2002). The contribution of environmental factors to these diseases is considered to be at least equal to genetic factors, as concordance of autoimmunity in monozygotic twins ranges from 15 – less than 50% (Cooper GS et al., 1999). Environmental risk factors have generally been poorly studied, and these diseases are also thought to be increasing in frequency (Jacobson, DL et al, 1997) likely due to the increasing contribution of novel environmental triggers. Environmental risk factors have most often been identified in anecdotal reports and related by temporal association with onset of disease. These have occasionally been confirmed or better substantiated in case-controlled epidemiologic investigations (Cooper GS, et al. 2002). Environmental risk factors identified to date include most commonly a number of infectious agents, breast feeding (type I Diabetes mellitus, JRA), ultraviolet light (SLE, juvenile dermatomyositis), as well as certain drugs or biologic agents, including vaccinations. This area of research has been largely unexplored, particularly in childhood-onset autoimmune diseases.

Examination of autoimmune diseases as a component of the Children's National Health Study could take several venues, with some hypotheses unique to autoimmunity and some that interface with other study hypotheses that are proposed in other working groups.

Possible Hypothesis 1. To generate an estimate of the incidence of autoimmune diseases in childhood.

The incidence of specific autoimmune diseases has not been well studied. Most specific disease incidence estimates are based on small, regional cohort studies that are both underpowered to estimate incidence and are not representative of the entire US population. Few to no nationwide incidence or prevalence cohorts exist for any single autoimmune disorder, let alone the collection of autoimmune diseases. For example, studies of the incidence of JRA, ranging from 4 – 11 cases/100,000/year (reviewed in Cassidy and Petty, 2001), have all been based on regional cohort studies, the most recent and methodologically rigorous conducted by the Mayo clinic in a rural county of Minnesota (Peterson et al., 1996). National estimates or estimates in racial/ethnic groups other than Caucasian are not available.

The study could examine the incidence of a selected number of autoimmune diseases throughout childhood. NHANES similarly provided new data on the prevalence of arthritis and musculoskeletal disorders in a national cohort (Lawrence RC et al., 1998). As a nationwide, prospective cohort of 100,000 children, it represents the largest and most representative sampling available to date. A diagnosis of a new autoimmune disease might be captured in questionnaires (with a listing the most common disorders to capture). Confirmation of the new diagnosis would be ideally captured through additional questions and/or through medical record review by an expert panel to confirm the diagnosis. Alternatively, all patients could be screened for new onset autoimmune diseases by using screening questionnaires; a connective tissue screening questionnaire is currently available, for example.

A potential offshoot of interest to this hypothesis is to examine whether the incidence of autoimmune diseases is increasing over time, suggesting a role for new environmental risk

factors. The estimates obtained from this study can potentially be compared to historical estimates, as well as to estimates from future studies.

Possible Hypothesis 2: Examination of specific environmental triggers in prospectively- collected samples. (vs focusing specifically on infectious agents in etiology of autoimmune diseases; concept is potentially broader than this, however)

If patients with specific autoimmune diseases are identified and biological specimens are collected prior to, as well as following illness onset, then these may be used to further develop data on association of certain environmental agents with autoimmune diseases. This may be particularly useful to explore the relationship of infectious agents to disease onset, although is potentially useful for bioassays of other environmental exposures as well. For example, in the NHANES cohorts, samples from patients with new-onset multiple sclerosis were examined for Epstein Barr and cytomegalovirus antigens and compared to unaffected age-matched controls, and EBV was found to be a risk factor for disease, based primarily upon blood collected before disease onset (Ascherio A et al., 2001).

Possible Hypothesis 3: Vaccinations are not associated with the development of autoimmune diseases.

Several routine childhood immunizations have been associated with certain immune-mediated adverse events. Of currently licensed vaccines, the most common of these associations include MMR and type I diabetes mellitus; rubella and arthropathy; hepatitis B and arthritis; and DPT and type I diabetes mellitus (reviewed in Chen RT, Pless R, DeStefano F, 2001). Most of these associations have been temporal and based on spontaneous adverse event reporting to the FDA VAERS system, although in some cases animal models suggesting biologic plausibility also exist. Limited case-controlled epidemiologic studies have either been underpowered to assess these events or inconclusive in their results. To further examine the

most common selected immune-mediated adverse events with vaccines, a priori time risk periods of disease susceptibility could be examined in the subjects in the Children's National cohort who receive these immunizations. Alternatively, comparison of relative risk of the events in patients receiving the vaccine vs. an age-, gender-matched cohort of subjects who did not receive vaccine or develop autoimmune disease could be attempted.

Possible Hypothesis 4: In utero and subsequent exposures to environmental agents that affect the endocrine system result in certain autoimmune diseases (interfacing with Hypothesis 5-7). Females, including those that are pre-pubertal, are more susceptible than males to many, but not all, autoimmune diseases (Beeson PB, 1994). Recent data suggest that hormonal factors from pregnancy and exogenous estrogenic hormones may be risk factors in human patients (Cooper GS, 2002; Lockshin, M, 2002). The reasons for this gender discrepancy in susceptibility are not understood. It would be of interest, particularly for diseases in which there is a female predilection, to examine for the presence of estrogen or LH/FSH disrupting agents prior to disease onset in affected vs. healthy control children.

Possible Hypothesis 5: Early exposure to bacterial and microbial products decreases the risk of autoimmune diseases (hygiene hypothesis) (interfacing with Hypothesis 4-5).

Similar to the allergic diseases, including asthma, infectious agents are also hypothesized to be protective for the subsequent development of autoimmune diseases, which is known as the hygiene hypothesis (reviewed in Bach JF, 2002). The hypothesis is further plausible as an explanation of childhood autoimmunity, since most children do not develop autoimmune diseases prior to 2 years of age. Circumstantial data for this hypothesis includes the fact that the increased incidence of autoimmune diseases has paralleled the rate of decline of certain infectious diseases. Additional epidemiologic data supporting this hypothesis include: 1) that the risk of multiple sclerosis is increased in individuals who spent their childhoods in

highly sanitized home environments (Leibowitz, 1996); 2) children with older siblings or those who attend day-care during the first six months of life subsequently have a lower incidence of type I diabetes mellitus (McKinney PA, 2000). Immunologic mechanisms for the protective effects of infections are also hypothesized (Bach JF, 2002).

Similar to examining the risk for asthma following early infections, the risk of a number of autoimmune diseases can similarly be addressed in children who are exposed to early infectious environments (day care, older siblings), who have increased numbers of infectious in the first year of life, or who are exposed to pets or a lower frequency of household cleaning etc., to see if infectious agents may be protective for the subsequent development of autoimmune diseases.

Possible Hypothesis 6, -3, Breast milk feeding, compared with infant formula feeding, and breastfeeding duration are associated with development of certain autoimmune diseases. (interface with Hypothesis 5-3)

Breast milk feeding has been reported to be a protective factor for the development of type I diabetes mellitus (reviewed in Cooper JJ, 2001) and adult onset- SLE (Cooper GS, 2002). In preliminary studies, breast milk feeding has been associated with protection against development of certain subsets of juvenile rheumatoid arthritis and risk with polyarticular disease (Rosenberg A, 1994). Breast milk feeding may have multiple mechanisms of protection or risk for disease: decreased early exposure to cow's milk protein, promotion of oral tolerance through passage of lymphocytes and immunoglobulins in breast milk; etc. It would be of interest to see if breast milk feeding and its duration are associated with risk or protection for various autoimmune diseases. A corollary to explore is whether excessive intake of soy-containing infant formulas, which are xenoestrogens, is a risk factor for subsequent development of autoimmune diseaes.

Note that a number of additional study possible hypotheses may be of interest to autoimmune disease outcomes: including:

2-1, Exposure to pesticides. Pesticide use in farming occupations has now been found to be a weak environmental risk factor for adult-onset systemic lupus erythematosus (Cooper GS et al., 2002). Studies in other autoimmune diseases or in children have not been conducted to date.

4-3, Maternal stress during pregnancy is associated with increased risk of asthma (autoimmune diseases)

4-4, Antioxidant constituents of diet decrease risk of asthma