Indian Heritage Childhood Diabetes Research: An Important Approach for Understanding the Etiology of Diabetes

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INTRODUCTION

Considerable strides have been made in the past decade in our understanding of the etiology and prognosis of childhood diabetes. Much of this work has been the result of a global network of scientists who have established a concerted approach to evaluate this disease in a systematic manner. The investigation of this disease in India will not only be important for the children of India, but also for our understanding of the disease process world-wide.

IMPORTANCE OF CHILDHOOD DIABETES

One of the modern miracles of medicine occurred with the identification and wide-spread utilization of insulin. Prior to insulin, the onset of childhood diabetes was a virtual death sentence. Children who developed this disease could be expected to live less than a year (1). However, with insulin mortality after the diagnosis fell from almost 100% to 6%, and is now less than 1% per year in most Western countries (2). This enormous increase in life expectancy is greater than that which has ever been seen for any chronic disease.

Despite the great promise of insulin, the hope that this drug would be the "cure" for the disease was short lived. As individuals who had the disease increased their longevity, chronic sequalae of the disease became evident. These complications included retinopathy, kidney failure, and neuropathy, which were rarely seen in the non-diabetic population. These complications and others painted a grim prognosis for the disease, even with insulin. Even in the 1980's people who developed the disease in the U.S. were still 5-11 times more likely to die than the general population (3).

In the past few years considerable interest has risen world-wide for coordinated investigations. There have been several reasons for the same. There has been the recognition that IDDM has major public health significance as childhood diabetes is one of the leading, if not the leading chronic disease, of children across the world (4). It is also a very expensive disease, such that by age 40, it costs over $50,000 per patient in the U.S. (5). Also, there is a considerable excess mortality associated with the disease, most of which is likely to be preventable (3).

India is an ideal country for investigations into childhood diabetes because of its diversity, major medical research traditions and leadership in the developing world. Here we describe information as to what is known about the etiology of the condition and what investigations in India could contribute to our understanding of the etiology and the prognosis of the disorder.

Childhood diabetes can be conceptualized as the product of environmental factors acting upon susceptible hosts to produce the disease. Unlike most other chronic diseases, more is known about the host-susceptibility factors than what is known about the environmental determinants.

In the late 1960's and early 1970's considerable interest was generated about childhood diabetes as strong associations began to be seen with specific genetic markers on chromosome 6 in an area called the Human Leukocyte Antigen (HLA) system. The initial reports indicated that HLA B8 and B15 were associated with childhood diabetes with a relative risk of 3-6 (6). Subsequent to this in the mid 1970's even stronger associations were seen to HLA DR3 and DR4 (7). It is of interest that similar associations have been seen in Indian populations (8,9), in various areas both within India and in South Africa (10). The association to specific antigens appears to vary depending upon whether the population is from north or south India (8,9). Overall in India and across the world the associations which have been seen with the DR loci have been in the range of 7-9 (7).

Much excitement has been generated in the past two years as it appears that scientists are narrowing the search for the susceptibility gene to

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a specific point on the DQ beta chain, such that in the U.S., people who are asp-57-negative appears to be over 100 times more likely to develop the disease than those who do not have this genetic characteristic (11). Initial reports from Madras also suggest than DNA markers appear to be related to childhood diabetes among Southern Indian populations to a greater extent than the serologic markers (12).

Recently it has been postulated that the prevalence of this particular genetic marker may explain why one population has a high incidence of disease and a second a low incidence (12). Clearly, additional studies such as within the diverse genetic background of India would shed important light on this issue.

Investigations into the environmental etiology of the disease have lagged behind the immunogenetic work. This is a shame because the identification of the environmental diabetogenic agents, and the reduction off these factors ,is likely to be the best approach for prevention of the disease as it is much more feasible less costly and safer than attempting to alter the immunologic milieu of a new onset adolescent IDDM patient or changing a person's genetic make-up to prevent the disease.

We believe that Indian heritage research will be important for understanding the etiology of the disease. The first step of Indian heritage research is to define the risk of developing the disease through the establishment of population based IDDM registries. This is important as through the development of registries, according to WHO guidelines (19), it will be possible to test the hypothesis that there are major regional differences in IDDM in incidence and the incidence of IDDM in India differs from other countries. The registries are needed to define the risk factors for childhood diabetes. A network of registries in India would also serve as an important source of information concerning the magnitude of the problem of childhood diabetes in India and would be available as a population source for more in-depth etiologic studies.

The beauty of doing epidemiological research in Indian is that India is like a microcosm of the world. The richness of genetic diversity is very evident. Moreover, because of religious and cultural tradition there has been only a limited degree of intermingling of ethnic groups, unlike for example, what is seen in the United States. Thus broad genetic hypotheses can be evaluated exclusively within India, which would be impossible in countries such as the U.S.

Perhaps the component which is most exciting scientifically in researching IDDM in India is the assessment of the contribution of environmental factors, to the susceptibility of disease. India here too offers unique advantages. For example, recently it has been suggested that meat and dairy products might contribute to an increased risk of disease (19), however this has not been examined in populations which are strict vegetarians as in seen in India. Similarly, viruses have been implicated as being associated with the onset of childhood diabetes, however these investigations have never been done in areas where there is a heavy burden of infectious disease, as could easily be accomplished in India.

Reports of the association of socioeconomic status (SES) to childhood diabetes have been weak (20). A difficulty has been that the places where the SES-IDDM relationship has been investigated have typically been where there is not a large gradient in socioeconomic status. In India, this association could be readily evaluated.

Indian populations are also very important for migrant studies, as large groups have moved to many areas across the world. Investigating the incidence of IDDM in Indian populations living on different continents, with different climates and diets, would likely provide important insight into the contribution of environmental factors and more specifically identify the specific environmental factors.

Thus considerable scientific information could be gained to understand the etiology of disease in children through the examination of childhood diabetes in India.

On a more pragmatic level, these investigations are likely to have considerable importance for the health of children in India. Currently there is little known concerning the magnitude of the problem of childhood diabetes in India. Establishment of diabetes registries in accordance to the guidelines developed through WHO will define for the first time the problems and needs for the children who develop diabetes in India. Inclusion of India in the World Health Organization Project for Childhood Diabetes will also raise the exposure of childhood diabetes in India(21). Having childhood diabetes in India officially a part of the WHO program would benefit research.

Of critical concern in developing countries is the possibility that at the onset of childhood diabetes, children are not diagnosed, and thus die. All of these deaths are essentially preventable. Through the establishment of a registry, the attention of physicians to childhood diabetes would be raised, and thus many more cases who develop the disease would be diagnosed, and salvaged. India can take the lead in this important area of investigation.

There are also opportunities for technology transfer through the development of an Indian program on childhood diabetes which is compatible with that of the WHO investigations. For example, the latest DNA technology is available for investigating IDDM and is readily transferable to India. The advantage is if the designs of research and the technology could be the same in India and other countries such as the U.S., the specific genetic probes could be made available to Indian scientists for collaborative evaluations. The transfer of DNA technology would have important implications not only for diabetes, but for all genetic work in the area of chronic disease.

Also, on a much broader level, childhood diabetes is a chronic disease which appears to have a viral etiology. The future health of India is dependent upon effective public health measures in the area of mid 1970's, and in Northern Europe, about a 3% increase per year for the past decade (15). The most striking example is midwest Poland with a virtual epidemic in the mid 1980's where the incidence doubled in only a short 2-year period of time (17).

The fourth argument is perhaps the most exciting. With migration, there appears to be a rapid increase in incidence (14). When low-risk individuals move to a "high" risk area, their incidence increases, which could only be accounted for by environmental factors. Dramatic evidence for this comes from Leicester, England. Upon expulsion from Uganda in the early 1970's the Asian population migrated to the U.K. (15). The incidence of childhood diabetes in this population shortly after arrival was very low, less than 1-2/100,000 (18). However, in a mere 15 year period the incidence rose over 10 fold. Thus it appears that the Asian population is at high risk of childhood diabetes, however, the risk is not expressed unless the population is confronted by a "diabetogenic" environment such as in the U.K. is hampered because of the lack of reliable data concerning the incidence of disease in the parent country of India.

The fifth argument is that at least in selected instances environmental factors such as viruses and toxins have been shown to produce childhood diabetes in humans (14). However the contribution of these specific factors has not been well defined.

Thus in the etiology of childhood diabetes exciting clues are being obtained as to the genetic contributions, but the environmental clues, are still, at best, vague.

There are several lines of evidence which suggest major environmental components to the disease. We thus know that the environment is extremely important, but we do not know what specific components of the environment actually produce the disease.

Twin data strongly imply a major environmental component (13), as only 36% of identical twins will become concordant of the disease. If genetics were the exclusive determinant, a much higher corcordance rate in twins would be expected.

We have argued that there are five lines of evidence which indicate that IDDM has a major environmental component (!4). The first is that IDDM can be produced in animal models with environmental factors such as chemicals or viruses.

The second argument is the extraordinary geographic differences in risk of disease (!4). Over all there is at least a 50-fold global difference in risk as a child in the Finland is over 50 times more likely to develop the disease than a child in China or Mexico. In the U.S., this would translate into the "prevention" of 12,500 of the expected 13,000 new onset cases of IDDM in children each year, if the risk of diabetes in U.S. children were the same as in Chinese children. Regretfully, we know nothing about the incidence of disease in India.

The third argument is that many populations have exhibited very rapid increases in the incidence of disease (15), in some areas of epidemic proportions. Finland for example has seen a 3-fold increase in incidence since 1950 (16). Investigations and potential preventive programs in childhood diabetes could have a major benefit the recruitment of the next generation of chronic disease investigators from the large pool of infectious disease scientists.

Therefore, much can be learned about childhood diabetes through the development of standardized research protocols in India that are directly comparable with efforts that have been established word-wide. Research in India on childhood diabetes would greatly increase our knowledge of the etiology would greatly increase our knowledge of the etiology of the disease for all children.

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