GENDER DIFFERENCES IN ISLET CELL REACTIVITY AND AUTOIMMUNITY IN INSULIN DEPENDANT DIABETES MELLITUS

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INTRODUCTION

Insulin dependent diabetes mellitus (IDDM) both in humans and in animal models is a multifactoral disease resulting from destruction of islet beta cells that leads to an absence in intrinsic insulin secretion[1]. The destruction of islet beta cells may be caused by autoimmune mechanisms, viral infection, chemicals, or introduction of transgenes into the beta cell, each in a setting of some genetic predisposition. Animal models, particularly the NOD strain of mice, demonstrate this form of IDDM [2,3].

IDDM in the NOD mice has an incidence of 80 – 90% in females, and about 20-50% in males. Insulitis is observed as early as 5 weeks of life, and is about 90% in NOD female mice and about 70% of NOD male mice at 9 weeks. The incidence and degree of insulitis increases with age resulting in beta cell destruction, loss of insulin secretion, hyperglycemia, a catabolic state and ketosis seen in human with uncontrolled IDDM. The female NOD mouse usually develops diabetes by the age of 6 months.

The NOD mouse spontaneously develops autoimmune Type 1 diabetes which is characterized by the presence of several autoantinbodies which is characterised by the presence of several autoantinbodies which serve as useful markers for predicting the development of diabetes, these include antibodies to the islet cells, viz, the cytoplasmic islet cell anti-bodies[4,5] and antibodies to glutamic acid decarboxylase [6,7]. IDDM may be accompanied by both organ specific and non organ specific autoimmune disorders[8]. The latter disorder includes the presence of autoimmune thyroiditis and sjogren's syndrome[2]. Future strategies for the primary prevention of IDDM in humans may be achieved by the oral administration of insulin as well as GAD-65[9]. The administration of oral insulin as well as GAD-65 has been demonstrated to delay the onset of diabetes in the NOD mice with a disproportionate effect in females[10,11].

We studied a cross section of subjects with IDDM with respect to the incidence of diabetes, islet cell reactivity and the concomitant presence of organ-specific as well as non-organ-specific autoimmune disorders with a view to ascertain whether the gender differences present in the NOD mice with IDDM were applicable to IDD's in humans.

SUBJECTS AND METHODS

A cross section of subjects with IDDM were studied in relation to sex distribution, the age of onset and duration of diabetes, islet cell reactivity (islet cell antibody and GAD-65 antibody), autoimmune thyroid disease (thyroid function and antimicrosomal antibodies), concomitant endocrinopathies (if any) and or connective tissue disorders. The results are reported as the mean ± standard error of the mean. The methodology for the essay of antibodies to the islet cells and GAD-65 are described elsewhere [12,13,14]. The student 't' tests was applied to the incidence of IDDM, the presence or absence of islet cell reactivity and autoimmune thyroid disease in the two sexes, A DIFFERENCE OF < 0.05 was considered to be of statistical significance.

RESULTS

The result of the study with respect to gender are presented as (I) Frequency of IDDM (ii) Islet Cell reactivity in IDDM (iii) Autoimmunity in IDDM and (iv) Gender differences in IDDM.

i. Frequency of IDDM

The study subject with IDDM (Females:20 (72.5%); Males: 8 (27.5%) had an age of onset of 16.5 ± 7.2 years (Range: 1.5 -–34 years) and a duration of diabetes of 6.6 ± 4.3 years (Range: 0.5 –12 years). Thirteen out of 17 subjects (76.5%) with childhood onset IDDM (age of onset less than 15 years) were females, including seven children with a preschool onset of IDDM.

ii. Islet Cell Reactivity in IDDM

Islet cell reactivity (Table 1) as either islet cell antibody or anti-antibody GAD-65 was observed in 16 subjects (57.1%) with IDDM. Fourteen subjects with IDDM demonstrated positivity to GAD-65 antibodies (median titre > 16) whereas ten subjects (35.7%) demonstrated antibodies to the islet cells (median titre 20 JDF units). Both antibodies were present in 9 subjects (32.1%).

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Table 1
Islet Cell Reactivity in IDDM (n = 28)

Antibodies	Positivity
Islet Cell or GAD-65	16
GAD-65 Antibody	14
Islet Cell Antibody	10
Both	9

iii. Autoimmunity in IDDM

Autoimmune thyroid disease was observed in 13/28 (46.4%) of subjects with IDDM of whom 12(92.3%) were females and only 5(38.5%) demonstrated islet cell reactivity. Hypothyroidism followed the diagnosis of diabetes and was detected on the basis of symptoms (n=7), recurrent hypoglycemic episodes with a decline in insulin requirements (n=4) and on routine investigations (n=2). Six subjects had multiple disorders in addition to IDDM and hypothyroidism (adrenocortical insufficiency and vitiligo = 1; non classical adrenal hyperplasia and vitiligo =1; lupus nephritis and rheumatoid arthritis = 1, myaesthenia gravis = 1; chronic active hepatitis and vitiligo = 1; vitiligo =2).

iv. Gender Differences in IDDm

The gender differences and islet cell reactivity in subjects with IDDM are shown in Table 2.

Table 2
Gender differences in Islet cell reactivity and autoimmunity in IDDM

Feature	Results		
	Female	Male	P value
Sex Distribution	20*	8	<0.001
Islet Cell Reactivity	11	5	<0.05
Autoimmune Hypothyroidism	12**	1	<0.001
Adrenocortical Insufficiency	1	0	ns
Non Classical Adreal Hyperplasia	1	0	ns
Vitiligo	3	4	ns
Myaesthnia Gravis	0	1	ns
Multiple Sclerosis	1***	0	ns
Rheumatoid Arthritis	1	0	ns

*6 Subjects with IDDM had multiple disorders .
**8 subjects with autoimmune hypothyroidism showed no evidence of islet cell reactivity. IDDM preceded hypothyroidism in all subjects.
*** The subject had an HLA DQB1 haplotype.

IDDM was observed in 20 female subjects (72.5%). Islet cell reactivity was observed in 16 subjects with IDDM of whom 11 (68.9%) were females. Autoimmune thyroid disease was observed in 13/28 (46.4%) of subjects with IDDM of whom 12(92.3%) were females and only 5(38.5%) demonstrated islet cell reactivity islet cell reactivity. Hypothyroidism followed the diagnosis of diabetes and was detected on the basis of symptoms (n=7), recurrent hypoglycaemic episodes with a decline in insulin requirements (n=4) and on routine investigations (n=2). Six subjects had multiple disorders in additions to IDDM and hypothyroidism (Adrenocortical insufficiency and vitiligo =1; non classical adrenal hyperplasia and vitiligo =1; lupus nephritis and rheumatoid arthritis = 1; myaesthenia gravis = 1; chronic active hepatitis and vitiligo = 1; and vitiligo = 2).

DISCUSSION

IDDM was predominantly seen in the female population with an earlier age of onset as opposed to the males. Islet cell reactivity was demonstrated by the presence of antibodies to GAD-65 and the islet cell in 57.1% of the subjects with IDDM and once again the majority were females (90.9%). Vitiligo was the most common non-organ-specific autoimmune disorder observed in subjects with IDDM, the male gender seemed to be more afflicted with this disorder (55.5%) as opposed to females. Six subjects had multiple disorders.

The frequency of IDDM in our study seems to be more common in the female sex as compared with the male (2.5 : 1) with an earlier age of onset as observed in the animal models of IDDM these observations are in keeping with our clinic records [15].

Islet cell reactivity as judged by the presence of antibodies to the islets of Langerhans (I.C.A. and antibodies to GAD-65) were observed in 57.1% of the subjects studied, majority of whom (68.5%) were females. These antibodies are useful in predicting IDDM and delineating the autoimmune nature of the disease [16], they may persist for many years in patients with polyendocrine disease including IDDM[17]. This is in keeping with our observations as 16 years after the onset of IDDM.

Autoimmune thyroid disease was seen in 46.3% of the subjects with IDDM screened for islet cell reactivity, amongst these, the majority (92.3%) were females. Hypothyroidism invariably followed the onset of diabetes, constipation was the predominant symptom in the preschool children. In others it was

recurrent hypoglycaemic episodes necessitating a reduction in the insulin dosage, thus mimicking the honeymoon phase encountered in IDDM's following in tensive therapy[18]. Recurrent hypoglycaemic episodes observed in hypothyroid subjects have been laid clearance of insulin because of hypothyroidism [20]. It is in this context that we emphasize the need for screening for autoimmune thyroid disease at diagnosis as well as during the honeymoon phase of served by us is particularly high when compared to a recent study on the frequency of Hashimoto's thyroiditis in children with IDDM[21]. They report a mean frequency of 3.9% with a female to male ratio of 4.5:1. The mean age of diabetes onset was 9.6 # 3.9 years, while age at hypothyroidism was 13.3 # 3.7 years. No autoimmune disorders were present although 29% subjects had a family history of autoimmune disorders (thyroid disease, IDDM and vitiligo). The small number of cases studied by us probably account for the increased frequency of thyroid disease as opposed to the a referred study [21]. Wherein a total of 1429 children with IDDM were studied, Vitiligo was observed in 7 subjects with IDDM were studies. Vitiligo was observed in 7 subjects with IDDM with a slight preponderance for the male (1.25 : 1) these subjects in addition to IDDM, had concomitant adrenocortical and thyroid deficiency and non classical / late – onset hydrolation defect of the adrenals with polycystic ovarian disease in the other. The latter condition may be due to the presence of autoantinbodies to the adrenals [22] or ACTH[23].

In conclusion, we would like to suggest that , the gender difference observed in subjects with IDDM in relation to there incidence, age of onset, islet cell reactivity and autoimmunity are similar to those encountered in animal models of diabetes [9,10,11].

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