

# Type 1 diabetes mellitus: Correlation between etiological factors and associated conditions

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**CONTEXT:** Genetic predisposition, autoimmunity, and viral infection are the main etiological factors implicated in the pathogenesis of type 1 diabetes mellitus (type 1 DM). **AIM:** To study the conditions associated with type 1 diabetes mellitus in the context of its etiological factors. **SETTINGS AND DESIGN:** Tertiary care centre; retrospective analysis. **METHODOLOGY:** We retrospectively analyzed all insulin dependent and ketosis-prone diabetic patients, with disease onset before 30 years of age, who presented to our center from 1997 to 2006. Details of history, clinical examination and relevant investigation reports were noted. **RESULTS:** A total of 214 patients (M: F 120:94) with type 1 DM were studied (mean age  $21.96 \pm 9.61$  years). Thirteen cases (6%) of hypothyroidism and two cases (0.9%) of hyperthyroidism were seen. Three patients of celiac disease were seen. Three cases of Turner's syndrome (1.4%), two cases of Klinefelter's syndrome (0.9%) and one case with bilateral optic atrophy (Partial Wolfram syndrome) were the chromosomal disorders noted. Three cases of cerebral palsy and two cases of deaf-mutism were encountered. Two cases with acute psychosis and six cases of depression were also seen. **CONCLUSION:** Autoimmune thyroid disorders, genetic disorders (Turner's syndrome and Klinefelter's syndrome), CNS disorders (cerebral palsy and deaf-mutism) were the associations encountered in the context of the etiological factors of type 1 DM. We might have under-estimated the extent of the prevalence of these associated conditions as the results of immunological and hormonal screening were not available in all cases.

**KEY WORDS:** Celiac disease, thyroid disorders, type 1 diabetes mellitus

The pathogenetic mechanisms in the causation of type 1 DM (autoimmunity, genetic factors and viral infections) may have a common link with the conditions associated with it (thyroid disorders, Turner's syndrome and cerebral palsy, respectively).

Genetic predisposition, autoimmunity, and viral infection are the main etiological factors implicated in the pathogenesis of type 1 DM.<sup>[1-3]</sup> These three factors may also contribute to the causation of the various conditions associated with type 1 DM.

Many of the patients with type 1 DM have associated autoimmune diseases like thyroid disorders, autoimmune adrenal disorders, celiac disease and connective tissue disorders, e.g. systemic lupus erythematosus (SLE).<sup>[4-6]</sup> Genetic disorders like Turner's syndrome, Klinefelter's syndrome, Wolfram syndrome and Down's syndrome are also associated with the type 1 DM. Slow viral infections, leading to central nervous system involvements like deaf-mutism, may have a common link with the viral infections implicated in the causation of type 1 DM.<sup>[7-9]</sup>

Although there are studies in Western populations on type 1 DM and its associated conditions,<sup>[10]</sup> few such studies are known in the Indian population.<sup>[11,12]</sup> This clinical study was planned to assess the associations of type 1 DM in the context of its various etiological factors and to study the possible common link between them.

## Methodology

We retrospectively analyzed the patient database of our diabetic clinic from the months of May 1997 to May 2006. All insulin requiring and ketosis-prone diabetic patients with disease onset before 30 years of age were included. Patients with a history of ketoacidosis or undetectable fasting C-peptide levels (if available) were also included in the study.

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Any patient with diabetes that was detected after 30 years of age was excluded from the study. Patients who were off insulin for more than three months were also excluded. Patients with a strong family history of diabetes but with only mild to moderate hyperglycemia (not requiring insulin) were presumed to have young type 2 DM or maturity onset diabetes of the young (MODY) were, accordingly, excluded from the study.

Available details regarding age of detection of diabetes; anthropometric data; sexual maturity rating (as per Tanner's staging); and findings on general and systemic examination (including dysmorphic features, goiter, features of target organ dysfunction, other endocrinological abnormalities, autoimmune organ dysfunction and neurological abnormalities) were noted. Available details regarding fasting and postprandial blood glucose, glycated hemoglobin (HbA<sub>1c</sub>), urinary ketones, serum electrolytes and arterial blood gas analysis, chest X-ray, ultrasound abdomen, thyroid function tests, fasting C-peptide and karyotype were recorded. Results of hormonal assays, including LH, FSH, estradiol, testosterone, prolactin and cortisol, in cases where they were clinically indicated, were noted.

## Results

A total of 214 patients of type 1 DM were studied [Table 1].

### Genetic disorders

Three cases of Turner's syndrome and two cases of Klinefelter's syndrome were seen in our series. There was one case with bilateral optic atrophy without deafness or diabetes insipidus (Partial Wolfram syndrome). Growth

retardation and pubertal delay was the predominant problem in the case of Turner's syndrome and behavioral abnormality complicated management in the patient with Klinefelter's syndrome.

### Autoimmune conditions

Hypothyroidism and hyperthyroidism were noted in 13 and 2 cases, respectively. Thyroid dysfunction, especially hypothyroidism, was associated with growth retardation, pubertal delay and poor scholastic performance.

Three cases of celiac disease presenting with chronic diarrhea were noted, in whom the diagnosis was confirmed by jejunal biopsy. One case of systemic lupus erythematosus presented with a lupus flare-up which required therapy with glucocorticoids. There were no cases of Addison's disease.

### Neurological disorders

Three cases of cerebral palsy and two cases of deaf-mutism were encountered, in whom management of diabetes was complicated by poor diet compliance and glycaemic control.

There were two cases of acute psychosis and six cases of depression in this series. Behavioral abnormalities and poor compliance with advice on diet control and drug therapy added to the problems in the management of their disease.

## Discussion

Type 1 DM is characterized by autoimmune destruction of beta cells precipitated by environmental insults in genetically susceptible individuals. Viral infections are

**Table 1: Type 1 diabetes mellitus and its associated conditions**

Associated condition	No. of cases (%) (n=214)	Clinical Impact
Hypothyroidism	13 (6.0)	Growth retardation, Pubertal delay, Poor scholastic performance
Hyperthyroidism	2 (0.9)	-
Papillary carcinoma	1 (0.45)	-
Celiac disease	3 (1.4)	Chronic diarrhea with difficult glycaemic control
Systemic lupus erythematosus	1 (0.45)	Difficult glycaemic control with glucocorticoid intake
Turner's syndrome	3 (1.4)	Growth retardation; pubertal delay
Klinefelter's syndrome	2 (0.9)	Behavioral problems
Wolfram syndrome	1 (0.45)	Visual deficit
Cerebral palsy	3 (1.4)	Additional health-care provider requirement; difficult diet and glycaemic control
Deaf-mutism	2 (0.9)	-
Acute psychosis	2 (0.9)	Difficult diet and drug compliance; behavioral problems; socioeconomic burden
Depression	6 (2.8)	-

known to be one of the initiating environmental factors. We have retrospectively analyzed cases of type 1 DM in our study, focusing on these three factors (genetic predisposition, autoimmunity and viral infection) in its pathogenesis and in the causation of its various associations. This may throw some light on the link between these conditions. The major histocompatibility complex (MHC) has been extensively studied in type 1 DM.<sup>[10]</sup> The human leukocyte antigen (HLA) genotype with the highest risk for type 1 DM is DR3-DQ2 and DR4-DQ8. Subjects expressing this genotype have a 5% risk for developing type 1 DM by the age of 15 years.<sup>[13,14]</sup> Studies have shown the co-occurrence of autoimmune and genetic disorders in association with type 1 DM.<sup>[10,11]</sup> The existence of disease-specific autoantibodies and predisposing HLA types in patients of type 1 DM makes them more prone to develop these associated autoimmune conditions. Knowledge about these associations and regular screening for them can help in their early diagnosis and management.

### **Autoimmune disorders**

Autoimmune thyroid disease (AIT) forms a major subset of autoimmune endocrine disorders associated with type 1 DM. As much as 20-30% of the population with type 1 DM expresses thyroid peroxidase (TPO) and/or thyroglobulin (TG) autoantibodies, whereas they are expressed in only 13 and 11% of the general population, respectively.<sup>[15]</sup> Long-term follow-up suggests that as much as 30% of patients with type 1 DM develop AIT. Hypothyroidism is present in 4-18% of subjects with Type 1 DM.<sup>[15]</sup> Hyperthyroidism is much less commonly reported, with a prevalence of 1%, similar to that in the general population.<sup>[15]</sup>

In our study, we encountered 13 cases of hypothyroidism, 2 cases of hyperthyroidism, and 1 case of papillary carcinoma of the thyroid. Hypothyroidism manifested with poor growth despite good glycemic control in these patients. Routine asymptomatic screening for thyroid antibodies and TSH can diagnose more of these cases.

Celiac disease is seen in 4.6-6% of patients of type 1 DM. Approximately 5-10% of subjects with type 1 DM are positive for endomysial antibody (EMA) or transglutaminase (TTG) autoantibodies and a significant proportion (up to 75%) have abnormalities on biopsy of the intestine.<sup>[16]</sup> Malabsorption can adversely affect overall glycemic control, leading to recurrent hypoglycemia and fluctuating insulin requirements. In our study we had three patients with prolonged diarrhea who were proven to have celiac disease by jejunal biopsy. One of them had

Turner's syndrome in addition.

Autoimmune adrenal disease is infrequently associated type 1 DM. Adrenal antibodies (antibody to 21-hydroxylase) are seen in approximately 1.5% of cases of type 1 DM, of whom 15% develop Addison's disease (AD) during follow-up. Overall prevalence of AD in type 1 DM has been reported to be 0.5%. Adrenal and thyroid autoimmunity coexist approximately 70% of the time.<sup>[5]</sup> We did not encounter any case of Addison's disease in our patients.

The autoimmune connective tissue disease, SLE, is uncommonly associated with type 1 DM.<sup>[17]</sup> In our study, we had a young boy with SLE complicated by anemia, lupus nephritis and vasculitis, who died during a lupus flare-up.

### **Chromosomal disorders**

Chromosomal abnormalities like Turner's and Klinefelter's syndrome are also reported with type 1 DM. Glucose intolerance in Turner's syndrome may become worse with obesity or during treatment with growth hormone or oxandrolone.<sup>[18]</sup> We encountered three cases of Turner's syndrome who presented with delayed puberty and short stature; one of them also had malabsorption due to celiac disease. Klinefelter's syndrome is classically known to be associated with abnormalities of glucose metabolism; about 19% of patients are reported to have impaired glucose tolerance and 8% have overt type 2 DM. We had two cases of Klinefelter's syndrome in our series, however, the causative link between type 1 DM and these conditions was not clear.

Wolframsyndrome (WS) is a hereditary neurodegenerative disorder defined by the association of young-onset, nonimmune, insulin dependent diabetes mellitus and progressive optic atrophy. Affected individuals may also present with other clinical features, particularly diabetes insipidus and sensory nerve deafness; hence, it is referred to as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). In a study of type 1 DM patients, 31 Lebanese patients affected with WS were detected, all derived from consanguineous marriages.<sup>[19]</sup> In our study we had one patient of type 1 DM with bilateral optic atrophy; however, he had no deafness or diabetes insipidus.

### **Neurological disorders**

Depression, anxiety and acute psychosis are the psychiatric conditions associated with type 1 DM. A

history of depression is associated with substantially worse glycemic control and more serious retinopathy than is seen in patients without psychiatric disorders. In our study we had two cases of acute psychosis and six patients with depression and suicidal tendencies. These patients had poor glycemic control and poor scholastic performance. They needed prolonged counseling and psychopharmacological therapy for better control of their psychiatric illness.

Since viral infections like coxsackie B, hepatitis C and HTLV-1 have been implicated in the etiopathogenesis of type 1 DM, there could be associated neurological disorders of probable or confirmed viral etiology with type 1 DM.<sup>[7-9]</sup> Some such slow virus diseases can give rise to cerebral palsy or deaf-mutism in type 1 DM. In our study we had three patients with cerebral palsy and two patients with deaf-mutism.

This study has the following limitations:

1. Only clinically overt associations were assessed; asymptomatic screening for antibodies or hormonal assessment of the associated conditions was not done. This must have resulted in underestimation of the prevalence of the associated conditions.
2. Being a retrospective analysis, all the cases could not be worked up completely.
3. Psychiatric conditions may not be directly related to the causative factors of type 1 DM; however, it is mentioned in view of its clinical importance.

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