

Type 1 diabetes mellitus in pediatric age group: A rising endemic

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ABSTRACT

Type 1 Diabetes Mellitus is the most common endocrinological abnormality found in children. The incidence of T1DM has steadily increased in nearly all parts of the world. Both genetic susceptibility and environmental factors contribute to the pathogenesis. It is caused due to either decreased or absent insulin production in the body due to multiple etiologies. We have done a literature review of type 1 DM in children and a clinical audit of point prevalence of type 1 DM cases & its clinical correlates of patients presenting at the tertiary level hospital, AIIMS Rishikesh, over two years six months period (April 2015 to September 2017). We found the prevalence of diabetes mellitus (Type 1) is 2.88%. Among clinical features at presentation, 56.5% presented with polyuria, 34.8% with polydipsia, 21.7% with polyphagia, 39.1% with weight loss. 26.1% of patients had diabetic ketoacidosis at presentation. The majority of children have deranged HbA1C levels (94.4%). It is concluded that children presented with higher HbA1c levels at onset and higher duration of symptoms are at greater risk for the development of complications.

Keywords: Diabetic ketoacidosis, HbA1C levels, lipodystrophies, type 1 DM

Introduction

Diabetes in children includes various causes of diabetes ranging from genetic basis, environmental, drugs or chemical induced, and infections. Still, all lead to loss of β -cell mass and functions, leading to impairment of effective glucose utilization.^[1-4] Incidence is continuously increasing worldwide, almost making it an endemic disease soon. The prevalence of diabetes is rising in India; as per International Diabetes Federation (IDF 2016), an increase of over 10 million was seen from the year 2011 to 2016, counting it to about 62 million. As per the latest update from IDF 2020, among all diabetic patients, 10% constitute type 1 diabetes mellitus. The most frequent type of diabetes seen in

children is type 1 diabetes mellitus. Type 1 DM is characterized by low or absent endogenous insulin levels and by dependence on exogenous insulin to prevent complications like diabetic ketoacidosis nonketotic hyperosmolar coma. Here, we had done a clinical audit at our tertiary hospital, AIIMS, Rishikesh, along with a literature review of Type 1 DM in children.

Clinical Audit

Aims

Point prevalence of insulin-dependent diabetes mellitus (Type 1 DM) and analysis of its clinical correlates in children attending tertiary care pediatric unit, AIIMS, Rishikesh.

Objectives

To estimate point prevalence of insulin-dependent diabetes mellitus (Type 1 DM) in children (0-18 years of age) and to analyze clinical correlates of type 1 diabetes mellitus.

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Materials and Methods

Study design

A retrospective study was conducted in the pediatric department of tertiary level hospital AIIMS Rishikesh. (clinical audit of children with diabetes mellitus).

Study duration

From April 2015 to September 2017, i.e., two years six months

Inclusion and exclusion criteria

From April 2015 to September 2017, i.e., 2 years 6 months, all the children admitted with diabetes were enrolled.

Methodology: We found 23 patients who are admitted with the diagnosis of type 1 DM. Their clinical features, including symptoms & signs, biochemical parameters, complications & treatment modalities, were documented in a computerized datasheet. Since, this is a retrospective audit so exempted from ethical approval as per institute policy.

Statistical analysis

All the data were analyzed using Epi inf software. The prevalence of Type 1 DM among admitted patients during the period was calculated. Percentages of clinical features at admission were analyzed by calculating percentages.

Results

Prevalence of diabetes mellitus (Type 1) is 2.88%. 9/23 (39.1%) female and 14/23 (60.9%) male with Type 1 DM [Figure 1]. 56.5% presented with polyuria, 34.8% with polydipsia, 21.7% with polyphagia, 39.1% with weight loss [Figure 2]. 26.1% of patients had diabetic ketoacidosis at presentation. 17.4% of patients had UTI as an associated complication. 17 patients out of 23 patients had deranged HbA1C levels, which is 94.4%. 3 out of 23 patients had a positive family history, two patients had a father with type 2 DM, and another had a positive history in both grandparents (paternal & maternal) of type 2 DM. 2 patients (10.5%) had poor compliance to management. 3 patients (13%) had lipodystrophies, Diabetic retinopathy in 4.3% & subcapsular cataract in 4.3%.

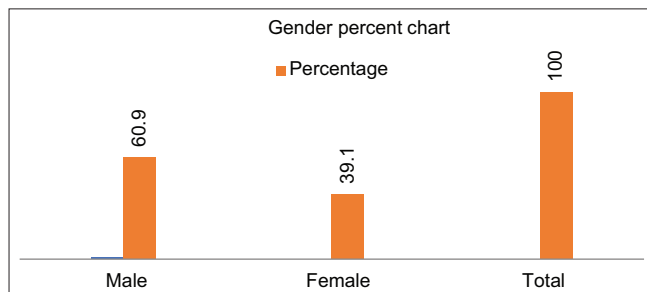


Figure 1: Gender distribution among total number of diabetic patients enrolled in this study

Discussion

Type 1 DM: characterized by low/absent endogenous insulin & dependence on exogenous insulin to prevent complications like DKA & NKHC. Menon *et al.*^[5] had estimated the prevalence of type 1 DM <1-3.6%, which is similar to the prevalence of Type 1 DM of 2.88% in our study. Karnataka state T1DM registry estimated that prevalence among boys was 3.7/100000 & girls was 4/100000 over 13 years, whereas in our study, 60.9% boys & 39.1% girls were affected. Kumar *et al.* had reported poor glycemic control in 10.7% of 39 (1040) patients only, whereas in our study HbA1c was deranged in 94.4% of patients, which is higher than Kumar *et al.*^[6] This can be explained as being it a tertiary care hospital only severe cases had been referred here, or there may be poor awareness about diabetes and its treatment in hilly areas here. Majaliwa *et al.*^[7] found in their study that 75% of children presented with diabetic ketoacidosis (DKA) at admission, which is higher than our study, which is 26.6%. In our study, we have found complications like lipodystrophy in 13%, diabetic retinopathy in 4.3% & subcapsular cataract in 4.3% which is lower than Kumar *et al.*^[6] who reported complications like retinopathy in 8.4% (14/166), neuropathy 5.2% (12/230), nephropathy 8.6% (20/230), hypertension 2.6% (6/230). This can be due to earlier reporting to our center for diagnosis at the onset of symptoms, so that time lag for the development of long-term complications was not there. Ahmed *et al.*^[8] have also reported long-term complications in type 1 DM like diabetic retinopathy in 33% of patients; he further found that these patients were those with longer diabetes duration ($p = 0.02$) and higher HbA1c levels. ($p = 0.009$).

Conclusion

The incidence of DM is 2.88%. The most common clinical feature was polyuria. 1/4th presented with diabetic ketoacidosis as the initial presentation. There was 3% who have a positive family history. The majority of children have deranged HbA1C levels. Diabetic retinopathy is found in 4.3% of patients, which can be prevented with early diagnosis and euglycemic management.

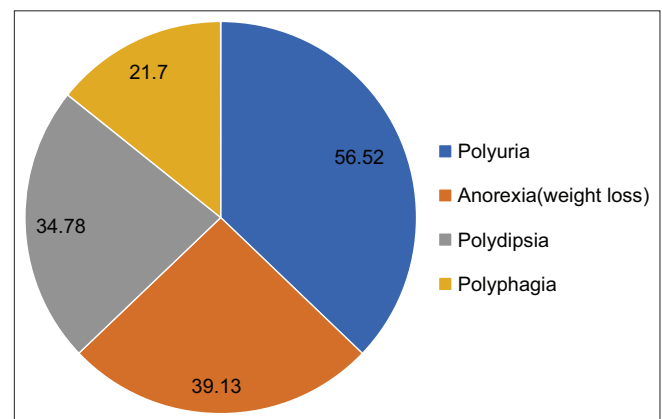


Figure 2: Pie diagram showing the percentages of clinical features among diabetic patients at admission

Review of Literature

Type 1 diabetes mellitus

INTRODUCTION: Type 1 Diabetes in children, also known as insulin-dependent diabetes mellitus earlier, has in common reduced or complete absence of insulin production due to autoimmune destruction of islet cells of the pancreas. The age of presentation is usually 6 to 16 years, with the recent change in the shift towards the younger population. Patient with type 1 DM needs lifelong insulin therapy for normal survival without developing any complications of diabetes. There are four phases of diabetes: pre-diabetes, diabetes, honeymoon period, and complicated diabetes. In the pre-diabetes phase, there is a persistent decline in insulin release due to β -cell destruction by auto-antibodies.^[1] During this period, autoantibody to β -cell antigens like insulin autoantibody (IAA), islet cell cytoplasm (ICA), antibodies to glutamic acid decarboxylase, and ICA512 are present in diabetic children. It is the pre-symptomatic phase that is seen after some insult in the background, due to which, after some time patient will start manifesting symptoms of diabetes.^[1] In the diabetes phase, symptoms may range from polyuria, polydipsia, polyphagia, weight loss, or weight gain. If the child is missed for diagnosis in this period, the child may progress to a transient remission period known as the honeymoon period. There is some release of insulin from the residual β -cell of the pancreas in the transient remission period. In the last phase child usually presents with signs/symptoms of DM and its complications, acute or long-term complications.

ETIOLOGY: The etiology of type 1 diabetes is broadly divided into immune-mediated and idiopathic. Major histocompatibility complex (MHC) is a large region of genes that regulates the immune function of the body. It is subcategorized into human leukocyte antigen (HLA) classes I, II, III, and IV genes. Around 50% of genetic variations in these MHC regions risk the development of type 1 diabetes.^[1,9] One major region associated is the binding of HLA proteins to peptides of antigens and their presentation to T-cells.^[1,10] Among these, HLA class II is linked most with the susceptibility to develop the disease. Whereas HLA I is associated with earlier onset of disease in a patient with type 1 diabetes. There is also positive family history in approximately 5% of patients with diabetes. It has been found the risk of developing the disease in a child is more if the father has diabetes as compared to the mother with diabetes.^[11] However, most children with type 1 DM do not have a positive history in their families, which points to some novice mutation or insult for the development of DM. Additional stress towards environmental factors leading to the development of type 1 DM has also been postulated. It has been seen that certain viral infections, mumps, and some enteroviruses lead to β -cell autoimmunity leading to the destruction of the pancreas. Diet and stress play their role in pathogenesis, but there is a lack of evidence to prove the mechanism.

PATHOGENESIS: When a patient with vulnerable genetic material is exposed to precipitating factors for diabetes

mellitus, which then trigger the pathogenesis for DM to be initiated. First, there is the formation of auto-antibodies to pancreatic β -cells, which leads to the destruction of β -cells. As the destruction of β -cells ensues, the synthesis of insulin compromises.^[1] It is postulated that 80% of the destruction of β -cells occurs before the disease manifests clinically. At the onset of clinical signs or symptoms, some viable β -cells may take over the function and secrete insulin, so there is a transient honeymoon period. But as it progresses further, the patient will manifest the disease or may later end up in complications due to DM. It has to be stressed here that in spite of the initial phase of autoimmune destruction of the pancreas, all patients don't manifest overt clinical DM. Besides, as the presence of a number of autoantibodies involved in the development of DM increases, there is a rapid progression of the disease process.^[12-14] Firstly, Insulin autoantibody (IAA) is formed, followed by glutamic acid decarboxylase 65 kDa, tyrosine phosphatase insulinoma-associated two, and zinc transporter eight later.^[15,16] It has to be stressed that how the course of the disease will progress is also based on individualization.^[12,17,18] Therefore, neither the pathogenesis nor the treatment should be based on "one for all."^[19]

CLINICAL MANIFESTATION: The appearance of clinical signs and symptoms occurred in the second phase of diabetes when insulin level decreased to moderate levels due to a progressive decrease in β -cells of the pancreas. Before this phase, although the process of destruction is taking place, the child won't show any symptoms. At this moderate decrease of insulin levels ensues catabolic state, only after feeding, leading to a reduction in peripheral glucose utilization by muscle and fat tissues resulting in postprandial hyperglycemia. As the disease progresses further to lower levels of serum insulin, it increases glycogenolysis and gluconeogenesis in the liver, resulting in even fasting hyperglycemia in the child. As the renal threshold of glycosuria exceeds, osmotic diuresis starts, and the child will develop polyuria. Further, the child develops nocturia and more intense polydipsia as chronic hyperglycemia supervenes. There is a loss of glucose (calories) in urine that results in starvation and the development of polyphagia in the child. Even though polyphagia does not cope with the amount of loss of calories in urine, the child presents with weight loss due to loss of fatty tissue.^[20] These all pathological events lead to an increase in levels of stress hormones. These contra-regulatory hormones are epinephrine, growth hormone, cortisol, and glucagon. In diabetes, these hormones cause metabolic decompensation, the ensuing increase in free fatty-acids production. Due to insulin deficiency and glucagon excess, the formation of ketone bodies (β -hydroxybutyrate & acetoacetate) from these free fatty acids occurs. In DM, the rate of ketone body formation exceeds their peripheral utilization and renal excretion leading to ketoacidosis, manifesting as fruity breath odour. The accumulation of ketoacidosis lands the child into diabetic ketoacidosis.^[20] At this moment child develops abdominal pain, nausea, and vomiting, Kussmaul respiration as the disease progresses. Compensatory rapid, deep breathing in

an attempt to excrete excess carbon dioxide results in Kussmaul respiration. As the condition worsens, the child develops a decline in neurocognitive function and coma. Although seen less frequently in children, nonketotic hyperosmolar coma can be one of the presentations, inpatient, with DM. Presenting with severe dehydration, nonketotic acidosis, Kussmaul respiration may or may not ketosis, seizures, or various neurological sign and symptoms.

DIAGNOSIS: Diagnostic criteria for diabetes mellitus: if any child presenting with signs and symptoms and has random blood sugar levels either 200 mg/dl or more is diagnosed as DM, or the child may present with fasting blood sugar of more than or equal to 126 mg/dl or postprandial levels (2 hours post-feeding) more than or equal to 200 mg/dl or glycated hemoglobin levels more than or equal to 6.5%.^[16]

Additional testing for diabetes: ABG (acid-base gas analysis), serum electrolytes, urine for ketones, serum osmolality are the tests that should be done in case of a child presenting with DKA or nonketotic hyperosmolar coma.^[16] Serum blood glucose levels more than 200 mg/dl, presence of ketonuria with blood pH <7.35, and pCo2 levels below 20 mEq/L points towards DKA. The presence of severe hypernatremia in patients with DKA suggests severe DKA. Nonketotic hyperosmolar coma can be diagnosed by blood glucose levels >800 mg/dl, may or may be mild ketosis and acidosis.

Autoantibodies for diagnosis of immune-mediated diabetes-like islet cell autoantibodies and autoantibodies to insulin, GAD (GAD65), the tyrosine phosphatases IA-2 and IA-2b, and ZnT8 should be considered in all cases of type 1 diabetes.^[16] Various studies have even shown that these autoantibodies also have a role in screening at-risk populations for the development of Type 1 DM, especially if a first-degree relative has diabetes.^[21] So, this can help to implement nutrition education and disease education to patients, thus having a role in primordial prevention. It can also help us in early diagnosis and prevention from complications if the child can be followed closely.^[22]

Testing for associated auto-immunities: In children, diabetes is associated with many other autoimmune diseases, so additional testing to rule out the same should also be done.^[16]

- Tissue transglutaminase & IgA levels: Coeliac disease
- Thyroid profile: Hypothyroidism
- Anti-thyroglobulin antibodies & anti-thyroid peroxidase: Thyroiditis.

If done timely, management of these autoimmune diseases in all cases of diabetes mellitus, can improve the overall prognosis.

COMPLICATIONS: The degree and duration of hyperglycemia much influence the development of complications. So, early diagnosis, intensive management of hyperglycemia, and prevention of hypoglycaemic episodes can reduce diabetes

complications.^[23] All primary care should be motivated to do random blood sugar estimation of children coming with symptoms suggestive of early stage of the disease like, polyuria, polydipsia or sudden change in weight. Diabetic children should be managed in a way to reduce both hyperglycaemic and hypoglycaemic fluctuation, if the need arise should be referred aptly.

Due to insulin therapy: Psychological or behavioral problems due to self-testing or injections, lipodystrophy at the injection site, hypoglycaemic attacks.

Long-term complications: Microvascular complications include retinopathy or nephropathy. Macrovascular complications include cerebrovascular diseases, coronary artery disease, and peripheral vascular diseases. Peripheral and autonomic neuropathies can also be seen. It has been found in many studies that the longer the duration of symptoms with poorly controlled diabetes, there is a high risk of developing complications.^[7,24-28] [Table 1]

Conclusion: There is a rising burden of type 1 DM worldwide, which is further increasing due to lifestyle modifications. Early identification of symptoms, timely screening, and maintaining euglycemia should be prime to reduce the prevalence of complications due to diabetes.

Key points

- Routine screening by random blood sugar levels of all children with early symptoms like polyuria can help in early diagnosis.
- Auto-antibodies testing causing DM, in children with first degree of relatives suffering from diabetes, and lifestyle modifications can help in primordial prevention.
- Controlling the duration of hyperglycemic as well as hypoglycemic phase in patients can help to delay the development of long-term complications.

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Nil.

Table 1: Percentages of complications reported in various research articles of type 1 Diabetes Mellitus

Long term complications	Research article	Percentages
Diabetic retinopathy	Nordwall <i>et al.</i> ^[24]	27
	Majaliwa <i>et al.</i> ^[7]	22.7
	Mayer-Davis <i>et al.</i> ^[25]	17
	Salardi <i>et al.</i> ^[26]	56.2
	Ramachandran <i>et al.</i> ^[27]	13.4
Nephropathy	Nordwall <i>et al.</i> ^[24]	5
	Demirel <i>et al.</i> ^[28]	16.1
	Ramachandran <i>et al.</i> ^[27]	7.1
Neuropathy	Nordwall <i>et al.</i> ^[24]	59
	Demirel <i>et al.</i> ^[28]	0.6
	Ramachandran <i>et al.</i> ^[27]	3
	Coronary artery disease	Demirel <i>et al.</i> ^[28]
	Ramachandran <i>et al.</i> ^[27]	1

Conflicts of interest

There are no conflicts of interest.

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