CASE CAPSULE

A 13-year-old boy presents to the outpatient department with complaints of tiredness and weakness. He complains that he is unable to concentrate on his schoolwork as well as his extracurricular activities since he gets tired easily. He also says his sleep is disturbed since he has to get up several times in the night to pass urine. His parents have noted that his clothes have lately started appearing loose on him. They are worried that all their friends and relatives remark that the boy has lost weight, in spite of having a hearty appetite.

What Further Questions Should be Asked in the History?

It should be ascertained whether the child had gained weight earlier, immediately preceding the onset of symptoms leading to weight loss. Symptoms related to other causes of weight loss like tuberculosis and thyrotoxicosis should also be elicited. Symptoms of malabsorption (steatorrhea) and recurrent abdominal pain should be asked for since these may provide a clue to the presence of chronic pancreatitis one of the causes of diabetes in youth.

The severity of symptoms is a poor guide to the type of diabetes. Although diabetes in children is usually symptomatic, it must be remembered that many cases are detected accidentally, while evaluating for other problems.

The parents state that the patient was a big baby at birth, weighing 4.6 kg. The mother does not remember being told that she had diabetes while she was carrying him. They also state that he has been always on the chubby side, but that he had recently gained a lot of weight. They attribute it to lack of exercise; the family has just moved to a new locality, and the child’s circle of friends was disrupted. He now spends most of his free time on the sofa watching TV. He does not have any history of productive cough or steatorrhea.

Both being a big baby (>3.5 kg at birth) or being, small for gestational age, if associated with rapid weight gain in infancy and childhood, are associated with increased risk of developing Type 2 diabetes in later life.
Would You Ask for a Family History of Diabetes?

This is the most important part of the history. One should get a family history going back at least three generations, on both sides of the family. Do not forget the siblings!

The parents tell you that they both have diabetes, diagnosed in their thirties. They are both overweight and are on oral antidiabetic agents. The patient has one sibling, an elder sister who has not yet been tested for diabetes. Both the maternal grandparents have diabetes as detailed below in the pedigree chart depicted in Figure 6.17.1.

Childhood onset Type 2 diabetes is usually associated with diabetes in either or both parents. Even if the parents do not give a history of diabetes, it is wise to screen them with a glucose tolerance test as they may have mild asymptomatic diabetes. Type 1 diabetes and secondary form of diabetes like fibrocalculous pancreatic diabetes (FCPD) are usually not associated with a positive family history.

Maturity onset diabetes of the young (MODY) is an uncommon form of monogenic diabetes caused by mutations in one or other of the genes controlling insulin secretion and beta-cell development. Maturity onset diabetes of the young is characterized by autosomal dominant inheritance, that is, the disease has to manifest in at least three consecutive generations. A young nonobese patient with a positive family history of diabetes confined to one side of the family going through two or more generation should be strongly suspected to have MODY.

What Would You Look for in the Physical Examination?

Patients with Type 2 diabetes are usually overweight or obese, even after accounting for the weight loss that might have occurred. They also tend to have markers of insulin resistance such as acanthosis nigricans and skin tags.

On examination, the patient was 152 cm tall and weighed 78 kg. His body mass index was 34.6 kg/m². He had acanthosis nigricans on the nape and sides of the neck. His blood pressure was 126/72 mm Hg.

Acanthosis nigricans is a marker of insulin resistance and the consequent hyperinsulinemia. It is a pigmented velvety lesion usually found at the nape and
sides of the neck and in the armpits shown in Figure 6.17.2. It can often be reversed with weight loss. It is typically found in Type 2 diabetes and is rare in Type 1 diabetes, FCPD and MODY. Patients with MODY, FCPD and Type 1 diabetes also tend to be nonobese or lean. Hypertension is not uncommon in children with Type 2 diabetes.

**What Investigations Would You Do?**

The first step is to confirm the diagnosis of diabetes. This can be done using an oral glucose tolerance test (OGTT) or a fasting plasma glucose test as given below in Table 6.17.1.

The OGTT should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 1.75 gm/kg body weight in children or 75 g anhydrous glucose dissolved in water in adolescents. The patient’s fasting and postprandial plasma glucose values were 202 mg/dL and 286 mg/dL, respectively. The glycosylated hemoglobin (HbA1c) value was 10.7%, indicating poor glycemic control for the preceding 2 to 3 months. His urine ketones were negative.

It should be emphasized that there is no relationship between the type of diabetes and the HbA1c values. Even though Type 1 diabetes is considered to be more severe than Type 2, patients with the latter form of diabetes also can have very high HbA1c values at presentation. Similarly, even though ketonuria is considered the hallmark of Type 1 diabetes, a patient with Type 2 diabetes can also occasionally present with ketones in the urine.

A fasting lipid profile is also often useful. The patients fasting lipid profile was as follows: Total cholesterol = 182 mg/dL, triglycerides = 220 mg/dL, high density lipoprotein (HDL) = 31 mg/dL, low density lipoprotein (LDL) = 107 mg/dL, very low density lipoprotein = 44 mg/dL.

Patients with Type 1 diabetes usually have normal lipid profiles except for hypertriglyceridemia, which can be profound particularly at onset of the disorder. In Type 2 diabetes, a mixed dyslipidemia is found, with low HDL, elevated triglycerides and normal or mildly elevated LDL.

A C-peptide assay is often useful to classify the type of diabetes.

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**Table 6.17.1: Criteria for the diagnosis of diabetes**

- If symptoms of diabetes are present along with casual (random) plasma glucose concentration equal to 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose 126 mg/dL (7.0 mmol/L)
- Fasting is defined as no caloric intake for at least 8 hours
- Two-hour plasma glucose 200 mg/dL (11.1 mmol/l) during an OGTT

**Keywords:** OGTT, Oral glucose tolerance test
The patient’s C-peptide values were 0.4 pmol/L (fasting) and 1.0 pmol/l (stimulated), indicating poor beta-cell reserve. The glutamic acid decarboxylase (GAD) antibody assay was negative.

One should be cautious while interpreting C-peptide values measured during periods of uncontrolled hyperglycemia. Due to the phenomenon of glucotoxicity, C-peptide levels may be temporarily suppressed during this time. In Type 2 diabetes, C-peptide levels can be expected to improve after control of hyperglycemia. In contrast, in patients with Type 1 diabetes, the C-peptide levels tend to decrease rapidly and become unmeasurable within a year after the diagnosis.

Patients with stable, new-onset Type 2 diabetes usually have good C-peptide levels for several years. In MODY and FCPD, the values are usually intermediate between Type 1 and Type 2 diabetes.

Another useful investigation is the GAD autoantibody assay. About 50 to 80% of patients with Type 1 diabetes are GAD antibody positive compared to less than 10% of Type 2 diabetes. Other antibodies which are found in Type 1 diabetes include islet cell antibodies and insulin autoantibodies.

Would You Screen for Diabetes Complications?

The American Diabetes Association recommends that all patients with Type 2 diabetes be screened for complications at the time of diagnosis. Hence, any child with Type 2 diabetes should undergo a retinal exam as well as a urine examination for microalbuminuria. The comorbidities of diabetes (dyslipidemia and hypertension) should also be looked for and treated.

What Would be the Line of Management?

Insulin and metformin are the only currently accepted modes of therapy for diabetes in the pediatric population. When there is extreme hyperglycemia, it is wise to start the patient on a short course of insulin until the glucotoxicity settles. Thereafter, the patient can be managed with metformin. Therapeutic lifestyle changes should be advised and reinforced at every opportunity.

The patient was started on a small dose of premixed insulin twice daily. He was intensively educated regarding diet and lifestyle changes, particularly the importance of insulin. Within 2 weeks the fasting and postprandial plasma glucose values dropped to 108 mg/dL and 125 mg/dL respectively and he felt much better. At this time, insulin was tapered off and he was initiated on metformin 500 mg BD. At the next clinic visit, his fasting and postprandial glucose values were 90 mg/dL and 102 mg/dL respectively. He was continued on metformin until his next HbA1c was obtained, which was 6.2%. At this time, metformin was tapered off and he was able to discontinue medication completely, 4 months after his index visit. His latest HbA1c is 5.7%. His C-peptide has improved to 1.0 pmol/l (fasting) and 2.6 pmol/L (stimulated).

His sister has been screened for diabetes and is fortunately normal. She has been advised regarding the ways to prevent diabetes.
The differential diagnosis of diabetes in childhood is usually straightforward, since most patients have Type 1 diabetes. However, with the burgeoning epidemic of Type 2 diabetes, it is likely that pediatricians will see more and more cases of Type 2 diabetes in their practice. The diagnosis of this condition requires a carefully taken history (focusing on family history) along with judicious use of investigations. The algorithm attached (Flow chart 6.17.1) explains the differential diagnosis of diabetes in youth in India.

**KEY MESSAGES**

- Maturity onset diabetes of the young is an uncommon form of monogenic diabetes. In young nonobese patient with a positive family history of diabetes, MODY should be strongly suspected.
- There is no relationship between the type of diabetes and the HbA1c values.
- A C-peptide assay is often useful to classify the type of diabetes.
- The comorbidities of diabetes should also be looked for and treated.
Fig. 6.17.2: Acanthosis nigricans