

Brittle diabetes

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Abstract

The term Brittle diabetes was first used by Woodyatt in 1938¹. The term has been commonly used since then to refer to a subset of diabetic patients who appear to have greater fluctuations in blood glucose concentration than the majority of diabetic subjects. These patients usually have type 1 diabetes mellitus and their high variations in blood sugar cannot be easily explained by any evident cause and after careful clinical management. Since clear guidelines for a precise definition are still lacking, this fosters insecurities concerning diagnosis and treatment of this condition. It is important to review the patient physically, biochemically and psychologically to determine the cause of 'brittleness'. There are often identifiable psychological influences triggering these conditions. Using a case study, the specific diagnostic and therapeutic approaches of 'brittle diabetes' are discussed. This case study of a patient with brittle diabetes shows how a close cooperation between internal, and psychological and psychiatric medicine units, and a combination of patient education and psychotherapy could be effective.

Introduction

Brittle diabetes is defined as 'metabolic instability sufficient to disrupt the patient's life', whatever the cause is². 'Brittleness' is a concept that is difficult to quantify and 'disruption of life' depends on the patient's usual life style and on various other independent factors. Therefore universally accepted diagnostic criteria are not available³.

Metabolic instability could be predominantly severe hyperglycaemia or hypoglycaemia or mixture of both. Emergency admissions due to poor diabetic control are much more common and prolonged in patients with brittle diabetes than in stable patients. The patients are usually young females but brittle diabetes is increasingly being reported in the elderly of both sexes, with the growing use of insulin in this age group⁴.

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Case report

A 38 year old female patient was referred to our unit for glycaemic control before a genito urinary surgery. Her medical records showed that she had diabetes mellitus for 3 years and she never achieved good glycemic control despite being tried on twice daily premixed insulin. She has had five previous admissions for diabetic ketoacidosis and three admissions for severe hypoglycaemia with loss of consciousness. Lately she was changed to a combination of metformin 1000 g tds, gliclazide 160 mg bd and pioglitazone 30 mg OD. Her Fasting Blood Glucose was 23 mmols. Her Body Mass Index was 19 kg/m².

Two years back she had had a premature and prolonged labour at 27 weeks, and delivered a large baby by caesarean section; sadly the baby died perinatally. There after she developed stress urinary incontinence for which she was investigated and various methods of treatment were attempted without good results. In addition she had several admissions for recurrent urinary tract infections. Allergic skin reactions have been documented for several drugs including glibenclamide, tolbutamide, amoxycillin, penicillin, nalidixic acid, beef and pork insulin.

A diagnosis of 'Brittle diabetes' was made. She was started on basal bolus regime using human regular and bovine lente insulin; after this she complained of severe itching and symptoms of hypoglycaemia. Although she was complaining of hypoglycaemic symptoms, blood glucose was still high. There was no skin rash at injection sites as she claimed.

When she actually had hypoglycaemia her main meals were found untouched in the bedside cupboard.

At home, she looks after her husband who is bed ridden after road traffic accident. The cause of 'brittleness' in this case was deliberate interference of treatment in order to escape difficult family situations. She was referred to the psychiatric unit and she underwent psychotherapy with very good immediate results. She had normoglycemia on three daily soluble insulin and beef lente insulin at bed time without any complications including allergic reactions. We plan to continue a combined specialised diabetic and psychiatric follow up.

Discussion

The best approach to brittle diabetes is to look for causes that may lead to wide swings in plasma glucose concentrations.

Insulin resistance

Requirement of insulin dose of more than 2.0 U/Kg/day indicate a significant underlying problem in a non obese adult patient. This could be due to apparent or genuine insulin resistance.

Puberty is an insulin resistant state mainly because of increased growth hormone secretion at this time⁵. In children with type 1 diabetes puberty is often marked by a rise in glycemia and increased insulin requirement.

Insulin sensitivity is impaired in obesity and physical inactivity. Excessive insulin dosage per se can lead to worsening obesity, and insulin resistance with poor metabolic control. A vicious cycle of increasing body weight and increasing insulin requirement occurs mainly in type 2 diabetes⁶.

Infection that is serious enough to cause fever often induces acute hyperglycaemia and an increase in insulin requirement. Chronic infections like tuberculosis, occult infection in the diabetic foot or abscesses associated with colon and kidney can some times result in insulin resistance leading to brittle diabetes.

Endocrine disorders causing excessive secretion of counter regulatory hormones (acromegaly, Cushing's syndrome, thyrotoxicosis, and pheochromocytoma) may not be clinically obvious in a diabetic patient with worsening hyperglycaemia.

Drugs such as glucocorticoids and β -agonist can cause insulin resistance, although this is usually mild.

Apparent insulin resistance is commonly due to the patient deliberately taking less insulin or not taking insulin altogether, to prevent obesity or to escape difficult situations at home or work⁷. Eating disorders like anorexia nervosa or bulimia and related problems like self induced vomiting, laxative and diuretic abuse may be present⁸. Narcotic drug addiction can lead to brittle diabetes by causing metabolic instability especially during the stressful period of drug withdrawal, when hyperglycaemia and ketoacidosis are common.

Problems with insulin absorption, distribution or clearance are rare and proven in exceptionally rare instances. Lipohypertrophy, induced by repeated injections in the same site can impair subcutaneous absorption of insulin, but the effect is small⁹.

Insulin antibodies could develop for impure insulin which can bind insulin and form immune complexes and reduce the circulating levels. With the wide spread use of purified and particularly human insulin this problem is now disappearing¹⁰. Insulin receptor and post receptor defects have been attributed to severe insulin resistance in a few patients¹¹.

Table 1. Causes of severe hyperglycaemia in spite of insulin treatment

Errors in injecting insulin

Inappropriate dosage or timing
Air drawn up in the syringe
Poor injection technique
Wrong insulin dosage

Defects in insulin pharmacokinetics (All are very rare)

Binding by insulin antibodies
Excessive insulin clearance
Genetic defects in or beyond insulin receptor

Defects in insulin action

Insulin receptor defects – rare
Post receptor defects – obesity,
Type 2 diabetes
Drugs – Glucocorticoids, Beta-agonists, narcotics
Counter regulatory hormone disturbance – Puberty (increased GH secretion)
– Dawn phenomenon (Somogyi effect)
Endocrine hypersecretion syndromes – Cushing's, acromegaly, hyperthyroidism, pheochromocytoma
Infections – TB, abscesses, wound infection

Dawn phenomenon (Somogyi phenomenon) is a dramatic increase in early morning glycaemia which may be related to falling levels of circulating insulin and/or a rise in counter regulatory hormones during the night. This is initiated by excessive dose of insulin for the caloric intake or activity pattern there by causing nocturnal hypoglycaemia. The physiological response to hypoglycaemia is the secretion of counter regulatory hormones which in turn induce hyperglycaemia. Changing the insulin dosage or regimen should readily correct metabolic instability.

Recurrent hypoglycaemia

15 – 20% of patients with brittle diabetes present with recurrent hypoglycaemia. Compared to brittle patients with recurrent ketoacidosis, those with hypoglycaemia are older and of both male and female sex¹¹. In individuals with very strict glycaemic control, decreased symptom perception of hypoglycaemia occurs because of reduced counter regulatory hormone response after recent antecedent hypoglycaemia. This has been termed 'hypoglycaemia induced autonomic failure'¹². Diabetic autonomic neuropathy could cause or contribute to hypoglycaemic unawareness through complex mechanisms¹³. Beta blockers given for concurrent hypertension or ischemic heart disease can augment hypoglycaemic unawareness in a few patients¹⁴.

Gastro paresis is a cause of brittle diabetes which is often overlooked. Insulin therapy is designed to match the absorption of food to the absorption of insulin. Any mismatch between these two factors will lead to wide swings in blood glucose between hyperglycaemia and hypoglycaemia. Treatment of gastro paresis often results in improvement in blood sugar control¹⁵. Vomiting of any cause, malabsorption, notably coeliac disease which can be associated with type 1 diabetes can cause severe hypoglycaemia. Hypoglycaemia can be profound following pancreatectomy or chronic pancreatitis as loss of α cells impair the counter regulatory glucagon response. Advanced renal failure reduces clearance of insulin through kidneys and hypoglycaemia can occur if insulin dosage is not reduced. Endocrine gland failure (Hypopituitarism, hypoadrenalism, hypothyroidism) resulting in hormone deficiency also can cause hypoglycaemia.

Like hyperglycaemia, hypoglycaemia can be deliberately induced by surreptitious intake of insulin, avoidance of food, or excessive and inappropriate exercise. There could be underlying psychiatric or psychological problems.

Table 2. Causes of recurrent hypoglycaemia

Impaired awareness of warning symptoms – beta blocker treatment – over treatment with insulin
Adrenal insufficiency
Hypopituitarism
Chronic vomiting
Diabetic gastro paresis
Malabsorption
Loss of glucagon secretion (pancreatectomy, chronic pancreatitis)
Alcohol abuse

Mixed glycaemic instability

25% of all patients with brittle diabetes manifest mixed metabolic instability¹⁶. Most patients have no apparent cause though hypoadrenalism, chronic pancreatitis, pancreatectomy or recurrent infections like sinusitis, tonsillitis can cause a mixed metabolic instability. Most often mixed instability is due to inappropriate insulin regimen or life style. Idiopathic brittle diabetes refers to cases in which glycaemic instability has no obvious cause.

Management

It is essential to follow a logical protocol that initially excludes remediable organic causes. First step in evaluation of patients with brittle diabetes is checking the patient's diabetic education, treatment regimen, injection techniques and activity pattern. Frequent monitoring of blood glucose especially in the early hours of the day will help establish possible dawn phenomenon or Somogyi phenomenon.

Rise in insulin level and corresponding fall in blood sugar level can be determined following a test dose of insulin under controlled conditions. All patients with apparently unexplained insulin resistance have normal insulin and glucose profiles after injection of insulin under controlled conditions indicating non-compliance is responsible.

Investigations to exclude infections (WBC, ESR, CRP, UFR, and culture), narcotic drug addiction (urinary screen for narcotic drugs), and endocrine disorders could be undertaken whenever appropriate. Insulin antibodies and insulin receptor antibodies can be determined in special centres.

Should no cause for genuine insulin resistance is evident, and then the possibility of factitious insulin

resistance should be explored. A formal psychiatric and psychological assessment of the patient and the family may guide to the diagnosis.

Where there is predominant hypoglycaemia, an 8.00 am serum cortisol should be measured in patients who manifest signs or symptoms of adrenal insufficiency. Pituitary function tests, gastric emptying studies and tests for malabsorption are indicated when appropriate.

Management of brittle diabetes can be frustrating and demoralising to the diabetes team and the family. Mortality is high in these patients due to ketoacidosis, hypoglycaemia and severe complications like renal failure. Team approach involving diabetes specialist nurse, the physician, social worker, psychologist and the psychiatrist is probably the most likely to succeed¹⁷.

Intensive insulin regimens with multiple daily injections, Continuous Subcutaneous Insulin Infusion (CSII)¹⁸, Subcutaneous Implanted Infusion Pumps, Continuous Intravenous Insulin Infusion (CIVII)¹⁹, Continuous Intra Peritoneal Insulin Infusion (CIPII)²⁰ are a few methods which have been tested and proven effective in a few cases with specific characteristics.

For the brittle diabetes that is not controlled by the new strategies of insulin treatment, with poor quality of life and increased rate of diabetic complications, pancreatic transplant is considered with much reservation. Compared to whole pancreas transplant, islet transplant is a easier procedure, requiring only a transhepatic percutaneous injection under local anaesthesia²¹. Both procedures require immunosuppression and with modern immunosuppressive treatment, insulin independence can be reached in almost all patients and can be maintained in more than 70% in 2 years²².

By good organisation and delivery of medical care brittle diabetes can be detected early and effective treatment may avoid further complications in these patients.

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CME

Choose the correct and appropriate answers

1. Causes of poor metabolic control (high blood glucose) in Type 1 Diabetes:

- a. Diverticular abscess
- b. Coeliac disease
- c. Obesity
- d. Narcotic abuse
- e. Growth spurt

2. Endocrine causes of hyperglycaemia:

- a. Grave's disease
- b. Toxic nodular goitre
- c. Addison's disease
- d. Hyperparathyroidism
- e. Puberty

3. The following are common causes of poor systemic levels of insulin in patients on insulin:

- a. Lipohypertrophy
- b. Use of insulin exposed to heat
- c. Air in the syringe
- d. Skin resistance to insulin
- e. Mistaken lower dose of insulin

4. Causes of recurrent hypoglycaemia:

- a. Gastroparesis
- b. ACTH deficiency
- c. Self induced vomiting
- d. Alcohol abuse
- e. Delayed meals

5. The following are appropriate steps in investigation of patient with high fasting blood glucose:

- a. Midnight blood glucose
- b. Midnight cortisol estimation
- c. Reviewing the dose of intermediate acting insulin at bedtime
- d. Checking for response to a dose of insulin as an inpatient
- e. Urine full report

5. ABCDE

4. ABCDE

3. BCE

2. ABE

1. ADE

Answers: