Diabetes Mellitus 1

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- No objectives were given

Done By: Ahmad Taha Alkhiary,
Khalid abdullah aburas & Reem AlAgeel
Edited by: Rahaf Binabbad
Revised By: Ahmed Al Yahya

References: lecture notes, Davidson's & step up

Introduction

What is DM1 ?

- ➔ Diabetes mellitus is a clinical syndrome characterised by an **increase** in plasma blood glucose (hyperglycemia)
- ➔ Type 1 DM is characterized by a severe deficiency of insulin. (Patients require insulin to live)
- ➔ In diabetes mellitus, it's not about the disease itself , it's about the **complications** it causes.
- ➔ If we screen 10,000 child for DM1 , we will get 30 positive cases in Saudi Arabia.
- ➔ Type 1 DM is a genetic disease not a familial disease.
- ➔ DM1 is Not related to obesity.
- ➔ The more you go up in the world map the more is the incidence in that country.
- ➔ It has a certain period of the year where it increases "winter" (because of viral infections)
- ➔ In KSA we have two peaks of incidence, at age 9 and age 13.

(معلومة غريبة: هارون الرشيد مات وعمره بالثلاثينات بسبب Type 1 DM, حسب الوصف اللي ورد من المؤرخين انه في طريقه الى غزوة من الغزوات جاه DKA ومات بعدها بثلاثة أيام. يُعتقد أن اللي عنده كان "لادا".) "LADA: Late autoimmune diabetes of adults"

What is the difference between a genetic disease and a familial disease?

- ➔ **Genetic Disease**: **a single gene** responsible for a pathology. (e.g. Diabetes Mellitus 1)
- ➔ If there is an identical twin and one of them had DM type Ⅰ = The other one has 50% to be affected.
- ➔ **Familial Disease**: **a collection of genes** (Polygenic) from a previous generation passed to another generation (Hereditary) (e.g. Diabetes Mellitus 2)
- ➔ "Familial" is more related to inheritance than "genetic".
- ➔ If there is an identical twin and one of them had DM type Ⅱ = The other one 100% will be affected.
- ➔ DM1 is a genetic disease, not a familial one. (يعني لو وحده ولدها اتشخص بتايب1 وسألت ايش مصير طفلي الثاني؟ نقولها احتمال اصابته ما تختلف عن احتمال اصابة ولد جيرانكم, ليه؟ لأنه الوراثة ما تلعب فيه دور كبير)

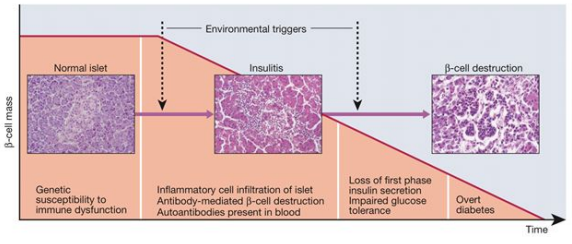
الزبدة: سواء تايب1 أو تايب2 كلها لها علاقة بالجينات. في تايب1 نعرف أنه يوجد جين واحد معيّن له علاقة بهذا المرض. لكن في تايب2 ما نقدر نحدد جين معيّن ولكن نقول أنه نتيجة خليط كبير من الجينات. الآن ايش اللي نتوقع له علاقة بالوراثة بشكل أقوى؟ تايب2! ليه؟ لأنه نتيجة جينات كثيرة تعطي تأثيرها بشكل أقوى.

Pathogenesis:

Autoimmune:

How is DM 1 a genetic disease ?

- ➔ On chromosome 6, short arm, segment **DR3 and 4** (a gene complex) will drive the mRNA to make something called **Islet cell antibodies (ICA)**, these antibodies will go through the blood circulation to reach the pancreas where they attack and cause an inflammation (**Insulitis**) & destruction of **Beta cells** thus causing insulin deficiency (hypoinsulinemia).



- ➔ Among 13 persons who have DR3 and 4, only one gets the disease.

(وجود segment DR3 and 4 في جينات شخص معين لا تعني بالضرورة أن الشخص هذا لازم يجيه DM1 ، ليش ؟ لأنه لازم يصير activation لهذه السيجمينت عشان تتكون الICA اللي تدمر خلايا بيتا في البنكرياس. طيب كيف يصير الاكتفيشن هذا ؟ عن طريق عوامل بيئية ⬇)

Environmental:

- ➔ An infection with **mumps virus** or **coxsackie B virus** will trigger B lymphocytes to produce antibodies (to fight the viral infection off), so as the mRNA starts transcripting antibodies against the virus it will also activate segment DR3 and 4 which will produce the **Islet cell antibodies (ICA)**.

DR3 and 4 could also be activated spontaneously (with no apparent reason), but mumps or coxsackie virus are the **most common** causes of activation.

Clinical Presentation:

- ➔ The main symptoms: polyphagia, polydipsia , polyuria and weight loss. **(MCQ)**
- ➔ **Onset:** typically in youth (before age 20). Although, It can happen at any age.
- ➔ Symptoms often develop quickly over days to weeks. "Acute" . **(MCQ)**

TABLE 4-5 Symptoms of Diabetes Mellitus

Symptom	Cause
Polyuria	Glucose in renal tubule causes osmotic retention of water, causing a diuresis
Polydipsia	A physiologic response to diuresis to maintain plasma volume
Fatigue	Mechanism unknown, but probably due to increased glucose in plasma
Weight loss	Due to loss of anabolic effects of insulin
Blurred vision	Swelling of lens due to osmosis (caused by increased glucose)
Fungal infections	Fungal infections of mouth and vagina common—*Candida albicans* thrives under increased glucose conditions
Numbness, tingling of hands and feet	Neuropathy Mononeuropathy: due to microscopic vasculitis leading to axonal ischemia Polyneuropathy: etiology is probably multifactorial

DM1 is ALWAYS acute, why? because as soon as the ICA reach the Beta cells the inflammation starts, and the destruction of beta cells will develop very quickly. Compared to DM2 where the person becomes hyperglycemic for a period before they undergo hyperosmolar hyperglycemic state.

- ➔ Sometimes appear after an illness.
- ➔ Patients often present with acute **DKA (MCQ)** (Diabetic Ketoacidosis → presence of ketone bodies circulating in blood & secreted in urine "beta-hydroxybutyrate"). Usually accompanied by hyperglycemia.
- ➔ DM 1 is in younger age, it is immunological, it is acute and it involves DKA. **(MCQ)**

How does diabetic ketoacidosis happen?
In short: In DM1, since there is severe insulin deficiency there will be a shifting of metabolism from Glucose metabolism (glycolysis) toward fatty acid metabolism which leads to production, accumulation and building up of ketone bodies resulting in diabetic ketoacidosis(DKA). **(it will be explained better in " DM complications " lecture)**

Signs and symptoms of DKA:

- ➔ Polyuria, Polydipsia
- ➔ Abdominal pain ± Nausea, vomiting*
- ➔ Dehydration (depletion of 6L, depletion
- ➔ Fruity breath زي ريحة الأسيتون (مزيل طلاء الأظافر) والأسيتون ماهو إلا كيتون
- ➔ Kussmaul breathing (a form of hyperventilation, to compensate for the acidosis)
- ➔ Mental changes (confusion, coma)

*Why DKA causes abdominal pain? there are some theories: Hypovolemia causes ischemia, acidosis causes the muscles to spasm, hyperkalemia causes distention and paralysis of the gut, neural stimulation plays a role. Result = pain & vomiting.

Diagnosis:

Sensitivity & specificity:

- ★ A **sensitive test** for **screening**, (to remember it: sensitive screen شاشة حساسة) when it is **positive** that means you **might** have the disease. When it is **negative** that mean **for sure you are normal**.
- ★ A **specific test** is for **diagnosis**, when it is **positive** that means the **disease is present**. When it is **negative** that means you **might** be normal.

diabetes tests		
Test	**SENSITIVITY**	**SPECIFICITY**
Fasting blood sugar	-	+
Random Blood Sugar	+	-
OGTT (oral glucose tolerance test)	+	+
Hb1Ac	+	-

الدكتور رسم الجدول هذا بنفسه في المحاضرة وركز على الفرق بين الاختبارات هذي ومتى نستخدمها وقال إنها موضع أسئلة اما بالنسبة للHbA1c الدكتور قال إنهم يحاولون يبعدون عنه لان قيمته في التشخيص ضعيفة فما يستخدم الا في المتابعة والمراقبة "HbA1C isn't that valuable for acute presentations like DM1"

⬤**Random Blood Sugar** → sensitive test → good for screening → when negative, rule out the disease.
⬤**Fasting blood sugar** → specific test → good for diagnosis → when positive, the disease is present.
⬤**OGTT (oral glucose tolerance test)** → sensitive & specific so it is the best confirmatory test. (but it is expensive & time consuming) غالبًا ما يستخدم إلا لمّا يكون التشخيص غير واضح أو مع سكر الحمل

Management

"First management is fluid, fluid, fluid!! because when they present to you most likely they're showing signs of DKA which might cause death by hypovolemic shock (polyuria, vomiting → dehydration).

After fluids you think of insulin" management of DKA in details will be discussed in diabetic complications.

1) Insulin

Rationale:

- ➔ Insulin is the main treatment and cornerstone of type 1 management.
- ➔ Type 1 diabetics start out deficient of insulin (the disease actually isn't evident until 90% of functional beta cells are lost) that's why we start them immediately on insulin. (unlike type 2)
- ➔ Insulin "switches off" ketosis & restores normal metabolic state.
- ➔ The cleavage of C-peptide (proinsulin → insulin) happens inside the Beta cell once glucose is sensed. (thus C-peptide levels correlates with the residual beta-cell function)
- ➔ Previously we used to take the insulin from animals like pigs and cows يجمعون البنكرياس الخاص بها و يستخلصون منه الانسولين, that wasn't practical. now with the development of genetic engineering, we synthesize insulin using E. coli & yeast. نخليها مصانع انسولين بالتالي نقدر ننتج كميات ضخمة.
- ➔ Insulin clearance is done by kidneys, so doses are reduced in Renal failure. "وحده من أعراض أن المصاب بالسكر بدأ يدخل برينل فيلير أنه يحتاج نقلل جرعة الانسولين حقته"

Method of administration:

- ➔ **Self-administered by SC injection in abdomen, buttocks, arm,leg.**
- ➔ **Given intravenously or IM for emergency ketoacidosis.**

Why not orally?

The human insulin is a dimer of an A-chain and B-chain,which are linked together by **disulfide bonds**. if you take orally stomach acid will break it down and inactivate it.

Insulin preparations			
Ultra short acting insulins	**Short acting insulins**	**Intermediate acting insulin**	**Long acting insulin**
Lispro, Aspart	Regular, Humulin	NPH, Lente	Glargine, Detemir

الدكتور ما أعطى الأسماء المختلفة لكن اهتم وركز على أهمية اختيار الأنواع المناسبة لمحاكاة وظيفة البنكرياس الطبيعية طول اليوم, مثلا Long acting في المساء وباقي اليوم ياخذ short acting قبل كل وجبة (قبلها بـ20د) أو أي خلطة أخرى مادامت في الأخير تحاكي نمط الإفراز الطبيعي للبنكرياس.

2) Diet & lifestyle modifications

Rationale:

- ➔ Like type 2 patients people with type 1 will need diet and exercise to improve their chances against complications.
- ➔ Similar modifications to type 2 patients.

الفكرة هنا هي ان اللي عندهم تايب 1 معرضين لنفس المضاعفات حقت 2 ولان مرضهم يبدأ من عمر أصغر عادة تجيهم ابكر فراح يستفيدون اذا ابتعدوا عن كل الأشياء اللي ممكن تسرع حصول المضاعفات هذي زي التدخين والسمنة وإلخ..

3) Beta cells transplantation

Types:

- **A- Beta cells transplant:** it is very effective way of treatment and can cure patient but it has some problems
  - For each patient we need pancreas of 2 brain dead individuals.
  - The transplant will start to dysfunction after 5 years.
  - The patient need to be on immunosuppressant.
- **B- Whole organ transplant:** you can't do it with a pancreas alone the patient must have another organ to be planted with it (liver,kidney) so it is only viable if the patient had a problem with other organs e.g type 1 with renal failure.

MCQs

---

1) Diabetes type1 is known to be link to which gene?

a. HLA DPRI.
b. HLA DQ2.
c. HLA DQ8.
d. HLA DR3-4.

2) What is the most common side effect of insulin in type 1 diabetic patients?

a. Lipohypotrophy.
b. Lower limb edema.
c. Skin Allergy.
d. Skin hyperpigmentation.

3) Which one of the following is associated with the destruction of B cells in type one diabetes?

A. Genetics.
B. Familial.
C. Congenital.
D. Drugs.

4) what is the best test to screen the population for hyperglycemia ?

a. OGTT (oral glucose tolerance test).
b. Fasting blood sugar.
c. Random Blood Sugar.
d. HbA1c .

5) The cornerstone of type 1 diabetes management is?

a. Beta cell transplant.
b. Metformin.
c. Diet.
d. Insulin.

6) A 20-year-old, Saudi University student presented with abdominal pain, nausea, vomiting, and weight loss. His blood sugar was found to be 18.3 mmol/dl, his blood gases revealed PH 7.1, PCO2 30, HCO3 10, his urine examination showed ketone bodies.
Which one of the following is the appropriate management?

A. Oral hypoglycemic target.
B. Insulin and IV fluid.
C. Strong analgesics.
D. Antiemetics.

Answer key:

1 (D) | 2 (C) | 3 (A) | 4 (C) | 5 (D) | 6 (B) |