Pitfalls In Diagnosis And Treatment Of Type 1 Diabetes Mellitus In Childhood

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INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic condition characterized by persistent hyperglycaemia due to absolute or relative insulin deficiency. According to the recent classification published by the American Diabetes Association in January of 2007, T1DM can be classified into two subgroups: Immune mediated and Idiopathic [1].

T1DM natural history is characterized by the intersection of multiple factors like genetic predisposition and environment. In a recent meta-analysis more than 40 distinct genomic locations provided evidence for association with T1DM. HLA genes present the strongest known association and there is a linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci, with both susceptible and protective haplotypes [2, 3]. The main known cause of the disease is however the progressive T-cell mediated autoimmune destruction of the β cells of the pancreas, manifested by low or undetectable plasma levels of C-peptide. Serological markers of this autoimmune pathologic process (islet cell, GAD, IA-2, IA- 2β , or insulin autoantibodies) are present in 85-90% of children when fasting hyperglycaemia is detected [4, 5]. The environmental triggers (chemical and/or viral) that initiate pancreatic beta cell destruction remain largely unknown, but process usually begins months to years before the manifestation of clinical symptoms [6,7]. Enterovirus is considered one of the most involved pathogens, due to its detection in the islets of individuals with diabetes; such viral

infection has been associated with development of diabetes associated autoantibodies [8,9].

Type 1 diabetes incidence varies greatly between countries, within countries, and between different ethnic populations. A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months [11]. The real incidence in African countries is still unknown [12]. However the incidence of the disease is worldwide increasing [13].

T1DM Diagnosis: difficulties in symptoms interpretation

Diagnostic criteria for T1DM are the same for children, young people and adults and are characterized by fasting glycaemia › 126 mg/dl (› 7.0 mmol/L) or postprandial glycaemia › 200 mg/dl (›11.1 mmol/L).

Symptoms of marked hyperglycaemia include polyuria, polydipsia, weight loss, sometimes with polyphagia and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycaemia. Clinical presentation of diabetes can vary from non-emergency presentations to severe dehydration, shock and diabetic ketoacidosis. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycaemia with ketoacidosis or the nonketotic hyperosmolar syndrome [13-15].

Sometimes it is difficult to distinguish T1DM onset: most of the symptoms are difficult to be recognized because subjects are usually healthy children with no previous problems. Failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis. Some children have a rapid onset of symptoms and present within days with diabetic ketoacidosis (see below); other have a slow onset over several months.

Main T1DM symptoms could be confused as follow:

the recent onset of enuresis in a previously toilet-trained child may be misdiagnosed as a urinary tract infection or the result of excessive fluid ingestion;

polydipsia may be thought to be psychogenic or simply related to weather conditions, especially in summer;

vaginal candidiasis, especially in prepubertal girls, could be thought as a low urinary tract infection or as an immune-suppression;

vomiting may be misdiagnosed as gastroenteritis;

chronic weight loss or failure to gain weight in a growing child could lead to bowel and/or feeding problems;

abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon;

hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis).

Urinary "dipstick" testing for glycosuria and ketonuria provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose›11.1 mmol/L) rapidly confirms the diagnosis [13].

Diabetic Ketoacidosis (DKA): difficulties in management

The pathogenesis of DKA is summarized in Figure 1.

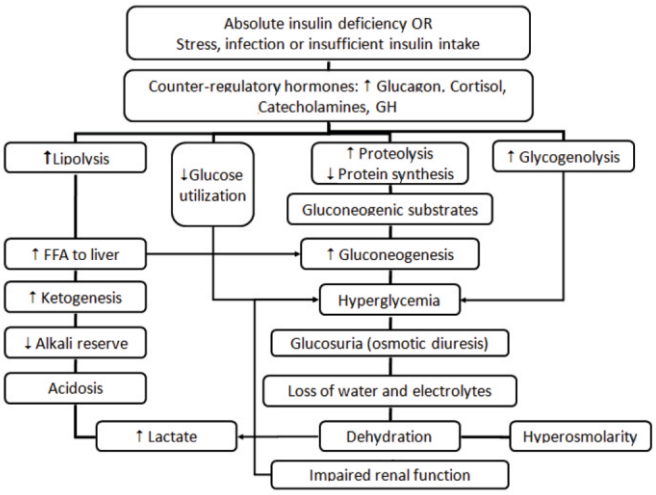

Figure 1: Pathogenesis of DKA.

If the cycle described in Figure 1 is not interrupted with exogenous insulin, fluids and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue. Diabetic ketoacidosis may present in different ways, often difficult to be recognised, as: severe dehydration, frequent vomiting with nausea and abdominal pain (that could mimic an acute abdomen), continuing polyuria despite the presence of dehydration, weight loss due to fluid loss, muscle and fat impairment, flushed cheeks due to the ketoacidosis, acetone detected on the breath, hyperventilation of diabetic ketoacidosis (Kussmaul respiration characterised by a high respiratory rate and large tidal volume of each breath), progressive loss of consciousness (disoriented, semicomatose or rarely comatose), shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis), hypotension (a late sign and rare in children with diabetic ketoacidosis), increased leukocyte count with left shift, non-specific elevation of serum amylase, fever only when infection is present [16-19].

The biochemical criteria for the diagnosis of DKA are: Hyperglycaemia (blood glucose ›11 mmol/L [≈200 mg/dL]), Venous pH ‹7.3 or bicarbonate ‹15 mmol/L, Ketonemia and ketonuria. The severity of DKA is categorized by the degree of acidosis and subdivided into three main categories [20]:

Mild: venous pH ‹7.3 or bicarbonate ‹15 mmol/L;
Moderate: pH ‹7.2, bicarbonate ‹10 mmol/L;
Severe: pH ‹7.1, bicarbonate ‹5 mmol/L.

DKA could present both at T1DM onset and in children with established diabetes. Management is summarized in Figure 2.

DKA presents several pitfalls, due to difficulties in diagnosis and in management. According to the norms of good clinical practice and following the international flow-charts presented below, many questions remain opened. It is important to bear in mind that the successful management of DKA requires meticulous monitoring of the patient's clinical and biochemical response to the treatment. First of all the patient with DKA has to be considered as dehydrated, remembering that Sodium blood levels are no indicative of the severity of the loss of fluids. The Corrected Na is calculated by: Measured Na + 2([plasma glucose mg/dl -100] /100) [21-23].

This is the real value of Na that has to be considered in clinical practice. The calculation of effective osmolality (mOsm/kg) is: 2 x (Na + K) + (glucose mg/dl / 18). Important adjustments have also to be considered [24,25] to fix the right amount of fluids and electrolyte replacement.

Insulin infusion has to be initiated after at least one or two hours from the fluids onset at the dose of 0.1 IU/Kg/hour and has to be maintained at least until the resolution of DKA [26,27].

Another important pitfall is the use of Potassium in fluids replacement. As well known, acidosis moves K+ from intra- to extra-cellular fluids and the child can be apparently normokaliemic, but it is important to keep in mind that in DKA a mean loss of K+ is estimated in 4 mEq/kg/bw.

However, depending on the biochemical data of the patients, a following scheme is suggested:

Hypokalemic: start potassium replacement at the time of initial volume expansion and before starting insulin therapy.

Normokalemic: start replacing potassium after initial volume expansion and concurrent with starting insulin therapy.

Hyperkalemic: defer potassium replacement therapy until urine output is documented.

The starting potassium concentration in the fluids should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements. The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/hr, subdivided to potassium phosphate and potassium chloride [16,28,29].

It is also important to underline that bicarbonate infusion is generally not needed in DKA: according to literature, severe acidosis is reversible by fluids and insulin replacement. Bicarbonate infusion has to be considered only in cases of severe acidemia (arterial pH at least ‹ 7.0), decreased cardiac contractility and peripheral vasodilatation and Life-threatening hyperkalemia with dosage of 1-2 mmol/kg over 60 minutes [30-32].

Last, but not least, one of the most insidious complications of DKA replacement therapy is the development of Cerebral Edema. The risk is higher in: younger age, longer duration of symptoms, severe acidosis, bicarbonate treatment for correction of acidosis, an attenuated rise in

measured serum sodium concentrations during therapy, greater volumes of fluid given in the first 4 hours, administration of insulin in the first hour of fluid treatment. Warning signs and symptoms to be evaluated are: development of headache and slowing of heart rate, changing in neurological status and/or specific neurological signs (e.g. cranial nerve palsies), rising of blood pressure and decreased of oxygen saturation. Treatment recommended is with Mannitol 0.5-1 gr/Kg over 20 minutes [16,33,34].

The management of DKA requires a lot of experience and a careful monitoring of the clinical conditions of the child, namely it's mandatory to avoid any rapid normalization of the biochemical values. A progressive slow recovery of normal values is generally the best strategy.

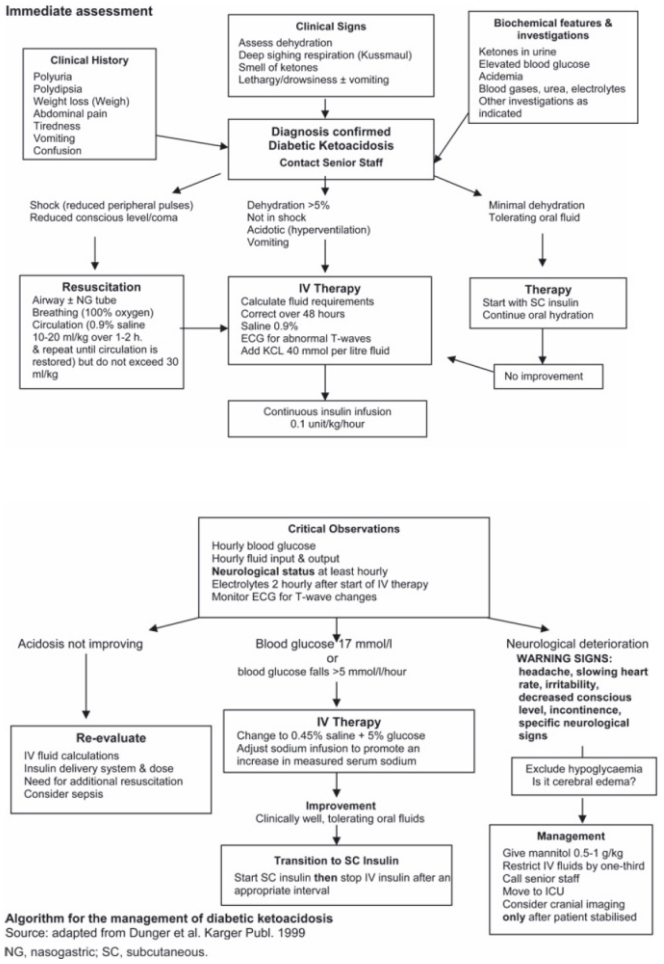

Figure 2 [16]: Flow chart of DKA treatment, according to The International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines. Management of DKA could be difficult because of the severity of acidosis: it is very important to proceed gradually starting with the clinical evaluation (to confirm the diagnosis and determine its cause), the measurement of weight and height (to determine the surface area), the assessment of dehydration and the consciousness level. In patients at high risk for shock we have to ensure advanced life supports as security of airways, vital signs monitoring, empty the stomach by continuous nasogastric suction, catheterization of bladder, oxygen, two peripheral intravenous catheter.

Blood and urine tests have to be rapidly performed, evaluating: glucose, renal function, Hemoglobin and complete blood count, Venous pH, pCO2, Electrolytes, Osmolality , Calcium, Phosphorus , Magnesium, HbA1c, ketones in urine, blood b-hydroxybutyrate concentration (if available). It is also important to collect specimens for culture (blood, urine, throat), if there is evidence of infection (fever) and to perform the electrocardiogram (ECG), for baseline evaluation of potassium status.

Insulin therapy: the role of age

Main kinds of insulin and procedures to manage the disease accordingly to different age are summarised in Tables 1 and 2.

Whatever might be the age considered, the main goal of T1DM treatment is to administer the right quantity of insulin to allow a normal growth and to maintain blood glucose levels in the right range to avoid hypoglycaemia and to obtain good glycosylated haemoglobin values.

From a practical point of view, however, the main goal is to allow a satisfactory social life of children and families, bearing in mind that the therapy must adapt to the life of the diabetic child and not vice versa [35].

Pitfalls of stable T1DM management could be subdivided into four main categories, accordingly to age:

Neonatal diabetes: The main goal of the therapy is to avoid hypoglicemia episodes. This is very complex to obtain due to the high number of meals (up to 7-8 feedings per day), the unpredictable food intake of neonates, the low amount of insulin with each injection, the extreme neonatal sensitivity to insulin, the vulnerability of the central nervous system to hypoglycaemia and the reduced neonatal glycogen stores. Initially phases of the treatment are based on the continuous intravenous administration of rapid-acting insulin at the dosage of 0.02-0.05 U/kg/hour, to be prolonged as long as possible before starting with subcutaneous administrations [35,36].

One to four years of age (Toddler): In addition to the most part of the pitfalls listed above, the toddler presents also the unpredictability of energy consumption due to the movement. These children spend a lot of time with different figures, like grandparents or nurses, who could have difficulties in disease management [35].

School age: This is the most stable age to manage T1DM thanks to the schematic daily routine of these patients [35].

Adolescence: This period is characterized by the physiological increased needing of insulin due to pubertal spurt. In addition, adolescence is characterized by behavioural problems, which could negatively influence the disease management. Patients usually show "rebellion" due to independence needing that lead to interruption of self-control practices and sometimes even of insulin injections. It is also presents a propensity to transgression with possible experiences of smoking, alcohol and drugs and, mainly in girls, eating disorders [36].

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Rapid acting analogs (aspart, glulisine, lispro)	0.15-0.35	1-3	3-5
Regular/soluble (short acting)	0.5-1	2-4	5-8
Intermediate acting Semilente (pork)	1-2	4-10	8-16
NPH (Neutral Protamine Hagedorn insulin)	2-4	4-12	12-24
IZS (insulin zinc suspension) Lente type	3-4	6-15	18-24
Basal long-acting analogs: Glargine Detemir	2-4 1-2	None 6-12	24 20-24
Long-acting: Ultralente type	4-8	12-24	20-30

Table 1: Summary of types of Insulin and Action Profile

Dietary recommendations: which is the best choice?

Diet management for children with diabetes is based on healthy rules suitable for the whole family, involved as active part in making appropriate lifestyle changes [37]. Nutrition and insulin regimen have to be adapted to cultural traditions, ethnicity and psychosocial need of

Ages	Insulin request	Insulin type	Number of subcutaneously administrations\day
Neonate\first year of age	0,25-0,5 UI/dose (6-8 meals)	Intermediate acting insulins associated or not to regular insulin	1 to 3 injections
One to four years of age	0,5-0,8 UI/Kg/die (40% have to be represented by basal insulinization)	**Basal insulinization:** Intermediate acting insulin in 2 or 3 administrations or long acting in one administration (now available for this age range) **Meals:** Regular insulin Or Rapid Acting Analogs	At least 3 injections
School age	0,7-1,0 U/Kg/die (40% have to be represented by basal insulinization)	**Basal insulinization:** Long acting **Meals:** Regular insulin Or Rapid Acting Analogs	3-4 injections
Adolescence	During puberty: 1,0- 1,8 UI/Kg/die After the spurt: 0.7-1 UI/Kg/die (40% have to be represented by basal insulinization)	**Basal insulinization:** Long acting in one **Meals:** Regular insulin Or Rapid Acting Analogs	4 injections

Table 2: How to manage diabetes according to different ages

children.
The main goal of the healthy diet is to provide sufficient and appropriate energy intake and nutrients for optimal growth and development. Total energy intake should be subdivided as follow [38]:
Carbohydrate: 50–55 % with moderate sucrose intake (up to 10% total energy)
Fat: 30–35%:
‹10% saturated fat + trans fatty acids
‹10% polyunsaturated fat
›10% monounsaturated fat (up to 20 % total energy)
n-3 fatty acids (cis configuration): 0.15 g /day
Protein: 10–15%

Three balanced meals per day with two appropriate healthy snacks could represent the best diet plan to maintain regular weight and glucose levels. Methods like the "Food Pyramid" (describing foods distributed in a pyramid, with the free eatable on the basis and, the more moving to the top, the less are the quantities) could be very useful to select the right food for each meal. Energy intake varies greatly within subjects on a daily basis due to age, growth rate, energy expenditure and environmental factors [36-38].
Recently a new method to manage the energy intake has been developed, called "Carbohydrate counting": a serious over-simplification suggesting that glycaemic control is only affected by the amount and type of carbohydrate [39].
In particular, for diabetic patients the most used method is the "Insulin-to-carbohydrate ratios", particularly appropriate for people on Multiple Daily Injections or insulin pump therapy. It involves the calculation of insulin-to-carbohydrate ratios that are individualized for each child according to age, sex, pubertal status, duration of diagnosis, time of day and activity. The ratio leads to adjustment of pre-meal insulin according to the estimated carbohydrate content of the meal. According to literature, the amount of insulin able to metabolize 15 gr of carbohydrates is 0.5-1 IU in adults. A practical procedure is to divide 450 (using regular insulin) or 500 (using rapid acting analog) by the amount of insulin in a day (IU): the result of the ratio is the quantity of carbohydrate metabolized by one IU of insulin[38-40].
Even if the method shows a good efficacy in adults with T1DM, its role in children is still controversial due to two main reasons:
post-prandial glucose is influenced by carbohydrates, proteins and lipids. By using the count it exists the high risk to consider only carbohydrates and to introduce an excess of calories due to the other main nutrients, or to develop a diet poor in proteins and lipids.
Children and families involved in carbohydrate count are often under an higher pressure, due to the difficulty to manage other important numbers in their daily routine.
The count used in children could be considered another pitfall in management of T1DM [38].

In conclusion, the management of the child with diabetes is a complex task already from the diagnosis and any doctor has to keep in mind that an early diagnosis allows avoiding fatal consequences.
The difficulties are present at any step of growth and they change year by year. The new device and insulin have made easier to manage this conditions improving the general quality of life, but the real improvement in the treatment can derive only by a progressive empowerment of the patient and their family.

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