Can J Diabetes 38 (2014) 225–228

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Case Report

Diabetes in Pediatric Patients with Kearns-Sayre Syndrome: Clinical Presentation of 2 Cases and a Review of Pathophysiology

Josephine Ho MD [a], Danièle Pacaud MD [a], Maja Rakic [b], Aneal Khan MD [c,*]

[a] Division of Pediatric Endocrinology, Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada
[b] University of Calgary, Bachelor of Health Sciences Program, Faculty of Medicine, Calgary, Alberta, Canada
[c] Metabolic Clinic, Department of Medical Genetics and Pediatrics, University of Calgary, Calgary, Alberta, Canada

ARTICLE INFO

Article history:
Received 30 January 2014
Received in revised form
4 April 2014
Accepted 7 April 2014

Keywords:
children
diabetes
mitochondria

ABSTRACT

Kearns-Sayre syndrome (KSS), resulting from a mitochondrial DNA deletion, is a rare cause of diabetes in children. We report 2 pediatric cases of KSS associated with diabetes that presented with hyperosmolar hyperglycemia with minimal ketosis. Both patients were treated initially with isotonic fluid resuscitation followed by intravenous insulin infusion.

The first case was a boy of Blackfoot Aboriginal ancestry who presented with failure to thrive, developmental delay and Fanconi syndrome and was diagnosed with KSS at 3 years of age. At 4 years he presented with a cough and left upper lobe lung infiltrate as well as a hyperosmolar hyperglycemic episode. He subsequently required multiple daily insulin injections. This patient developed cardiomyopathy and died at the age of 10 years.

The second case was a 6-year-old boy of Asian ancestry who presented with ataxia exacerbated by intercurrent illnesses, decreased exercise tolerance, gross motor and fine motor delays, anorexia and recurrent episodes of vomiting associated with dehydration, and he was subsequently diagnosed with KSS. At 11 years of age, the patient developed hyperosmolar hyperglycemia, and after treatment for it, he required multiple daily insulin injections. He died of end stage congestive heart failure secondary to cardiomyopathy at 13 years of age.

These 2 cases are presented to describe the possible pathophysiology of mitochondrial diabetes and to emphasize the need to monitor for the development of diabetes in patients with known mitochondrial disease and also to be aware of possible mitochondrial disease in pediatric patients who present with hyperglycemia in the context of multisystem involvement.

Mots clés :
enfants
diabète
mitochondries

RÉSUMÉ

Le syndrome de Kearns et Sayre (SKS) qui résulte d'une délétion de l'ADN mitochondrial est une cause rare de diabète chez les enfants. Nous présentons 2 cas pédiatriques souffrant d'un SKS associé au diabète qui ont présenté une hyperglycémie hyperosmolaire accompagnée d'une cétose minime. Les deux patients ont été initialement traités par réanimation liquidienne à l'aide d'une solution isotonique qui a été suivie d'une perfusion intraveineuse d'insuline.

Le premier cas était un garçon d'ascendance autochtone de la Nation des Pieds-Noirs qui présentait un retard staturo-pondéral, un retard de développement et un syndrome de Fanconi, et qui avait reçu un diagnostic de SKS à l'âge de 3 ans. À 4 ans, il a présenté une toux et un infiltrat pulmonaire au lobe supérieur gauche ainsi qu'un épisode d'hyperglycémie hyperosmolaire. Subséquemment, il a eu besoin de multiples injections quotidiennes d'insuline. Ce patient a développé une cardiomyopathie et est mort à l'âge de 10 ans.

Le second cas était un garçon de 6 ans d'ascendance asiatique qui présentait une ataxie exacerbée par les maladies intercurrentes, une diminution de la tolérance à l'effort, des retards de la motricité globale et de la motricité fine, une anorexie et des épisodes récurrents de vomissement associés à une déshydratation. Subséquemment, il a reçu un diagnostic de SKS. À 11 ans, le patient a développé une hyperglycémie hyperosmolaire pour laquelle il a été traité. Après ce traitement, il a eu besoin de multiples

* Address for correspondence: Aneal Khan, MD, Metabolic Clinic Department of Medical Genetics and Pediatrics Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary T3B 6A8, Alberta, Canada.
E-mail address: khaa@ucalgary.ca

1499-2671/$ – see front matter © 2014 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.04.003

injections quotidiennes d'insuline. Il est mort à l'âge de 13 ans d'une insuffisance cardiaque congestive terminale secondaire à la cardiomyopathie.

Ces 2 cas sont présentés pour décrire la physiopathologie possible du diabète mitochondrial et pour souligner la nécessité de surveiller le développement du diabète chez les patients souffrant d'une maladie mitochondriale connue, ainsi que pour sensibiliser à l'existence possible de la maladie mitochondriale chez les patients pédiatriques qui présentent une hyperglycémie dans le contexte d'une atteinte multisystémique.

Introduction

Mitochondria are the only intracellular organelles apart from the nucleus that contain their own DNA (mtDNA) encoding for a number of proteins critical for oxidative phosphorylation. The vast majority of mitochondrial proteins are encoded by nuclear genes with biparental inheritance, but the inheritance of mtDNA is almost exclusively maternal. Thus, mitochondrial mutations are matrilineal or de novo. There is a wide spectrum of clinical features in patients with mitochondrial diseases due to either nuclear or mtDNA mutations. Generally, tissues with high-energy requirements, such as the brain, heart, liver and skeletal muscle, are most affected by mitochondrial disease.

Inherited syndromes involving diabetes are estimated to make up about 5% of children seen in diabetes clinics (1). Diabetes due to mitochondrial disease can result from point mutations (maternally inherited diabetes and deafness, mitochondrial encephalopathy lactic acidosis and strokelike episodes); deletions or rearrangements in mtDNA (such as Kearns Sayre syndrome (KSS) or other deletion syndromes); or nuclear mutations (Wolfram syndrome, thiamine-responsive megaloblastic anemia). With mitochondrial deletion syndromes, such as KSS, Pearson syndrome and progressive external ophthalmoplegia, similar clinical features can be seen. In all cases, the clinical findings evolve over time, and some patients develop diabetes (1).

The classic triad of KSS includes retinitis pigmentosa, progressive external ophthalmoplegia and cardiac conduction abnormalities with an onset before 20 years of age. In addition to the triad, high cerebrospinal fluid protein or cerebellar ataxia may be present. Other clinical manifestations include short stature, diabetes mellitus, hypoparathyroidism, growth hormone deficiency, hearing loss, dementia and limb weakness (2,3).

We describe the clinical course of 2 pediatric patients with KSS whose diabetes presented with hyperosmolar hyperglycemia and minimal ketosis. In addition, we review proposed mechanisms for the development of mitochondrial diabetes.

Both families provided consent for the following case presentations.

Case One

A Blackfoot Aboriginal boy presented initially with failure to thrive and developmental delay at 12 months of age (Table 1). The pregnancy and delivery were reported to have been uncomplicated. The parents were nonconsanguineous and had no family history of any mitochondrial disorders. At 2 years of age, he developed renal tubular acidosis, hyponatremia, hypocalcemia and hypokalemia. He was diagnosed with Fanconi syndrome, and a chemical nephrectomy with indomethacin was attempted when he was 3 years of age. Subsequently, a left surgical nephrectomy was performed. This patient developed exocrine pancreatic insufficiency with steatorrhea and required replacement enzymes. Gastrostromy-tube feeds were also required to optimize nutrition. At 3 years of age he was diagnosed with KSS and found to have a 4977 base pair mitochondrial DNA deletion.

At age 4, he presented with a 1-week history of cough and suspected left upper lobe infiltrate. He was admitted to hospital and started on intravenous antibiotics. Two days later, he developed diarrhea and subsequent dehydration with a decreased level of consciousness. He was diagnosed with hyperosmolar hyperglycemia with minimal ketosis (Table 2) and treated initially with normal saline boluses to correct his dehydration. After 12 hours, the patient remained hyperglycemic, and an insulin infusion was started at 0.025 units/kg/hr. The insulin infusion was gradually

Table 1
Clinical characteristics of the 2 patients with Kearns-Sayre syndrome

	Case 1	Case 2
Gender	Male	Male
Age at diagnosis of mitochondrial disease	3 years	6 years
Ethnicity	First Nations	Asian
Genetic abnormality	4977 base pair mitochondrial DNA deletion	5000 Kb mitochondrial DNA deletion
Presenting features	Developmental delay, anemia, exocrine pancreatic insufficiency with steatorrhea, failure to thrive, Fanconi syndrome with renal tubular acidosis	Ataxia, muscle weakness, failure to thrive, Fanconi syndrome with renal tubular acidosis, macrocytic anemia, pigmentary retinopathy with visual loss, bilateral ptosis, myopic astigmatism, sensorineural hearing loss, cardiac pacemaker for bifasicular conduction block
Age at onset of diabetes	4 years	11 years
Age deceased	10 years	13 years
Antibody status at diagnosis	Anti-GAD antibody: negative Anti-islet cell antibody: negative	Not done
C-peptide status at diagnosis	2.43 nmol/L (0.4-1.4)	Not done
Total daily dose of insulin	0.5-0.8 units/kg/day	0.6-0.7 units/kg/day
Insulin regimen	Basal bolus (patient G-tube fed)	Basal bolus (patient G-tube fed)
Hemoglobin A1C range over last year	8.0%-9.4%	7.9%-9.4%

G, Gastrostomy; *GAD*, glutamic acid decarboxylase.