Intermittent Hyperglycemia due to Autonomic Nervous System Dysfunction: A New Feature in Patients with Congenital Central Hypoventilation Syndrome

Georges Gelwane, MD[1], Ha Trang, MD[2], Jean-Claude Carel, MD, PhD[1,4,5], Stéphane Dauger, MD, PhD[3,4,5], and Juliane Léger, MD[1,4,5]

Objective To analyze glycemic profile in children with congenital central hypoventilation syndrome, which is characterized by autonomic nervous system dysfunction.

Study design We carried out a university hospital–based observational study. Participants included 14 patients assessed from 2007 to 2009 with a median age of 7.6 (25th-75th percentiles, 1.5-9.6) years at the time of the study. Glucose metabolism was assessed by calculating 24-hour plasma glucose (before and after meals) and fasting insulin concentrations and carrying out an oral glucose tolerance test (OGTT). The main outcome measure was the proportion of patients with abnormal glucose concentrations.

Results Abnormal plasma glucose concentrations were found in 6 (43%) of the 14 patients with high fasting (n = 1) or postprandial (n = 5) hyperglycemia. OGTT was performed in 8 patients, of whom 3 (38%) had impaired glucose tolerance. Indices of insulin resistance and secretion were normal. No difference in clinical aspects relating to the presence of affected organs and/or systems related to central nervous system dysfunction, age, or auxology findings was found between patients with normal (43%) and abnormal (57%) glucose homeostasis over a 24-hour glycemia cycle or OGTT.

Conclusion This study provides new information about glucose homeostasis in congenital central hypoventilation syndrome, revealing a high incidence of hyperglycemia and expanding the spectrum of the disease. It highlights the link between autonomic nervous system dysfunction and glycemic dysregulation. Regular, long-term monitoring of glucose metabolism is recommended in these patients. *(J Pediatr 2013;162:171-6)*.

Congenital central hypoventilation syndrome (CCHS) is rare and may be life-threatening if undiagnosed or inadequately monitored and treated. Its incidence has been estimated at 1:200 000 births. About 1000 cases were identified worldwide in 2009, but this number is considered to be underestimated.[1,2] The disease is often diagnosed in the neonatal period, on the basis of alveolar hypoventilation with a weak response to hypercapnia and hypoxemia, but it may also be diagnosed later in childhood or in adulthood. CCHS is characterized by severe impairment of the central autonomic control of breathing and dysfunction of the autonomic nervous system (ANS). It is caused by a heterozygous mutation in the paired-like homeobox (*PHOX2B*) gene on chromosome 4p12, generally with a polyalanine expansion.[3] *PHOX2B* is expressed exclusively in the central and peripheral ANS.[4] Several other systems and organs innervated and regulated by the ANS are also affected, leading to a broad spectrum of possible clinical consequences.[5] Modern home ventilation techniques have increased the survival of most children with CCHS.

Insulin secretion by pancreatic β cells is stimulated by the parasympathetic nerves and their neurotransmitters. The activation of the sympathetic nerves leads to the inhibition, by norepinephrine and other neuropeptides, of insulin secretion. Glucagon secretion is stimulated by both the parasympathetic and sympathetic ANS.[6] Islet function is regulated in cycles, suggesting that the working of the islet as a functional unit is ensured by the synchronization of islet cells. Insulin is secreted in regular pulses by the pancreas.[7] The autonomic nerves may be responsible for this synchronization of the islets, which is of great clinical importance because both impaired glucose tolerance and type 2 diabetes are characterized by disturbed oscillatory patterns.[7]

Little is known about the metabolic features of CCHS. Abnormalities of glycemic regulation have not been studied in humans or *PHOX2B*-/- trangenic mice. However, hypoglycemia related to hyperinsulinism has been described in some

ANS	Autonomic nervous system
BMI	Body mass index
CCHS	Congenital central hypoventilation syndrome
FGIR	Fasting glucose-to-insulin ratio
OGTT	Oral glucose tolerance test
PHOX2B	Paired-like homeobox 2B gene
QUICKI	Quantitative insulin sensitivity check index

From the [1]Pediatric Endocrinology Service, Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, Centre de Référence des Maladies Endocriniennes Rares de la Croissance; [2]Physiology Service, Explorations Fonctionnelles, Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, Centre de Référence du Syndrome d'Ondine; [3]Pediatric Resuscitation Service, Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré; [4]INSERM, UMR 676; and [5]University Paris Diderot, Sorbonne Paris Cité, Paris, France

The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.06.036

subjects with CCHS.[8-11] We hypothesized that glycemic dysregulation, such as hyperglycemia or hypoglycemia due to abnormal insulin and glucagon secretion, would be observed in patients with CCHS, as a result of the continuous, congenital dysfunction of the ANS in these patients.

Methods

Since 2007, we have been conducting an observational prospective study at the CCHS national pediatric reference center at Robert Debré Hospital, Paris, France. For inclusion in the study, children had to have CCHS disease satisfying the following criteria: (1) persistent central alveolar hypoventilation during sleep, detected by polysomnography during the spontaneous breathing of room air; (2) no primary lung, neuromuscular, cardiac, or brainstem abnormalities that might account for hypoventilation; (3) absent or very weak hypercapnic ventilator responses[3]; and (4) confirmed genetic diagnosis of CCHS disease.

In total, 24 patients with CCHS were seen between 2007 and 2009. Those who did not undergo an assessment of glucose metabolism over at least one complete 24-hour glycemia cycle were excluded (nonparticipants). Such assessments were not carried out in these patients because they were too young or were in a critical condition. In total, 14 (56%) of the patients (participants) underwent evaluations of glucose metabolism, initially over one 24-hour glycemia cycle and then through an oral glucose tolerance test (OGTT), depending on the clinical status of the patient. Two of the participants (patients 3 and 8) were diagnosed late with CCHS, at the ages of 3 and 18 months, respectively. The other 12 patients were diagnosed during the neonatal period. All except 2 were white. The characteristics of the participants and nonparticipants, at the time of assessment, are shown in **Table I** (available at www.jpeds.com). Nonparticipants were slightly younger than the participants (median ages of 2.4 and 7.6 years, respectively; $P = .07$).

The clinical data for the patients were obtained from the patients' medical files. We collected data concerning ventilation support and its duration during the day; gastrointestinal diseases, such as Hirschsprung disease and esophageal reflux; and the presence of neural crest tumors, ocular and cardiac dysautonomia, and neurologic disorders. Weight was measured to the nearest 0.05 kg and height to the nearest 0.1 cm, by standard techniques. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Height and BMI are expressed as the SDS for sex and chronologic age.[12,13]

All patients underwent an evaluation of the glycemia cycle over 24 hours, after an overnight fast. This involved glucose and insulin determinations in the fasting state and glucose determination before and 1 hour after each of the 4 meals eaten during the day with a normal diet (breakfast, lunch, an afternoon snack, and dinner). Venous blood was also sampled at midnight and at 4 a.m. Glucose and insulin determinations were carried out at every feed for children under the age of 6 months fed only milk. For the OGTT, patients were asked to drink a glucose solution containing 1.75 g of glucose/kg of body weight (maximum of 75 g) within 5 minutes. Blood samples for glucose and insulin determinations were taken at 0, 30, 60, 90, and 120 minutes.[14] All subjects were clinically stable at the time of glucose metabolism assessments.

The study was approved by the institutional review board of Paris North Hospitals, Paris 7 University, Assistance Publique-Hôpitaux de Paris. Informed consent for the evaluation was obtained from the parents.

Impaired fasting glucose levels were defined as a fasting plasma glucose concentration of 5.6-6.9 mM.[15] Postprandial hyperglycemia was defined as a 1-hour postprandial plasma glucose concentration of >7.7 mM.[16] Hypoglycemia was defined as a plasma glucose concentration ≤2.8 mM.[17]

Normal glucose tolerance 120 minutes after loading was defined as a plasma glucose concentration of <7.8 mM, and glucose intolerance was defined as a plasma glucose concentration of 7.8-11.0 mM.[15]

Subjects were classified as having normal (group A) or abnormal (group B) 24-hour glycemia cycles. Five patients underwent OGTT to investigate glucose intolerance. Depending on the overall results of the metabolic assessment (glycemia cycle and OGTT), subjects were then classified as having normal (group I) or abnormal (group II) glucose homeostasis.

Insulin secretion was assessed by determining the ratio of the increase in insulin concentration over 30 minutes to the increase in glucose concentration 30 minutes after oral glucose loading.[18] Insulin resistance was defined in terms of various indices: (1) a homeostasis model assessment of insulin resistance >2.5. This index was calculated as follows[19]: fasting insulin concentration (μIU/mL) × fasting glucose concentration (mM)/22.5; (2) A fasting glucose-to-insulin ratio (FGIR) <4.5. This index was calculated as follows[20]: fasting plasma glucose concentration (mg/dL)/fasting plasma insulin concentration (μIU/mL) and; (3) A quantitative insulin sensitivity check index (QUICKI) of ≤0.34. This index was calculated as follows[21]: 1/log insulin fasting concentration (μIU/mL) + log fasting glycemia (mg/100 mL).

Assays

Glucose concentration was determined by the glucose hexokinase method, with an ADVIA 1800 analyzer (Siemens Healthcare Diagnostics, Saint-Denis, France). Insulin was assayed in an IRMA (Bi-Insulin IRMA, Cisbio International, Gif-sur-Yvette, France) in which there was no cross-reaction between intact and des-31,32-proinsulins. The detection limit was 3 pM and the intra-assay and interassay CV values were 3.8% and 8% for a concentration of 48 pM and 2.4% and 4.8% for a concentration of 300 pM.

Statistical Analysis

Data are presented as medians (25th-75th percentiles) for quantitative variables and as absolute numbers for qualitative variables. We assessed the significance of differences in clinical characteristics between participants and nonparticipants,