

Background

Youth type 2 diabetes (T2D) is increasing, linked with obesity and declining physical activity in high-risk population. In the United States, the prevalence of T2D in 2009 among adolescents aged 10 through 19 years was 0.46 per 1000 or 0.046%, with highest prevalence in American Indians, followed by black, Hispanic, and Asian Pacific Islander youths, with lowest prevalence in white ones. Studies in Europe indicate that T2DM remains rare in largely white populations. Insulin resistance (IR) plays a key role in the pathogenesis of T2D. Previously, we described that neurologically impaired (NI) children showed an unfavorable cardio-metabolic risk profile with a high prevalence of IR which was not related to BMI. In this brief report, we evaluated the prevalence of T2D in NI children and adolescents without obesity, in order to describe if a dedicated glucose profile monitoring may be recommended in this “fragile” population.

Patients and methods

We retrospectively evaluated 63 caucasian patients (35 M/28 F, mean age 11.4±4.0 years, range 1.9-19.1 yr) with severe disabilities (cerebral palsy 34.9%, epileptic encephalopathy 28.6%, severe psychomotor developmental delay in dysmorphic syndromes 36.5%). All subjects had been previously scheduled for surgical treatment (gastrostomy/digunostomy tube positioning, anti-reflux surgical treatment) and/or management of nutritional support devices.

Enteral feeding was adopted in 58/63 participants (bolus 82.7%, continuous pump feeding 17.3%) and oral feeding in 5/63 subjects (8%). Anticonvulsive drugs (at least two of the following: phenobarbital, valproic acid, phenytoin, lamotrigine, topiramate, carbamazepine and clonazepam) were reported in 56/63 (88.8%) of the whole sample; other therapies were recorded in 5 patients (in 3 anti-hypertensive drugs, in 1 growth hormone therapy, in 1 L-thyroxine). In all subjects physical activity was conducted for less than 60 minutes/week.

Methods

Clinical and anthropometric parameters

Physical examination of the subjects included anthropometric parameters as well as pubertal stage evaluation according to Marshall and Tanner (prepubertal characteristics corresponding to Tanner stage 1). Weight, height, waist circumference (WC) were measured as previously reported and consequently BMI and waist to height ratio (WHtR) were calculated.

Metabolic parameters

Metabolic blood assays included fasting blood glucose (FBG), insulin, triglycerides (TG). Insulin resistance was calculated with the homeostasis model assessment for insulin resistance (HOMA-IR). Triglyceride-glucose index (TyG index) was also evaluated using the formula $\ln[\text{fasting triglycerides (mg/dl)} \times \text{fasting plasma glucose (mg/dl)} / 2]$, as a surrogate marker of IR and predictor of diabetes,

Elevated FBG was defined with values exceeding 100 mg/dl and impaired insulin sensitivity (ISI) with a HOMA-IR exceeding the 97.5th percentile for age and sex. According to Vieira Ribeiro, TyG index was considered pathological with a cutoff exceeding 7.88.

T2D was defined as FBG \geq 126 mg/dL and/or 2-hour plasma glucose (PG) \geq 200 mg/dL and/or random PG \geq 200 mg/dL (in patients with continuous pump feeding only random PG \geq 200 mg/dL was considered) plus symptoms of diabetes (given the feeding difficulties, of these children, only polyuria was considered) and HbA1c \geq 6.5%

In diabetic patients the presence of islet autoimmunity (glutamic acid decarboxylase (GAD), islet antigen type 2 (IA2), anti-insulin (IAA) and zinc transporter 8 (ZnT8) autoantibodies) were excluded.

The waist to height ratio (WHtR) was then calculated with the standard formula and a cut-off of 0.5 was used to differentiate low from high WHtR.

Treatment following diabetes diagnosis was recorded.

Results

The average HOMA-IR was 3.5±0.6, with higher levels in pubertal compared to prepubertal patients (p=0.03) and without significant difference between sex (p=0.3). Insulin resistance was detected in 26/63 (41.3%) subjects, with a similar prevalence in males and females (p=0.7) and in prepubertal e pubertal subjects (p=0.1).

The mean values of TyG index observed in the sample was 8.1±0.75, which is higher in pubertal compared to prepubertal patients (p=0.03) and did not differ between genders (p=0.6). Pathological TyG index was noted in 40/63 patients (63.5%), without significant difference according to sex (p=0.3) and pubertal status (p=0.6).

No significant correlation between HOMA-IR and TyG was found (r=0.17 p=0.20)

Pathological FBG was detected in 7/63 children (11.1%), without difference between sex (p=0.3) and pubertal stage (p=0.09).

T2D was diagnosed in 2/63 patients (3.2%; 1 male and female with dysmorphic syndromes in which inborn errors of metabolism and mitochondrial disease were excluded) at the age of 4 and 8 years respectively. Both patients were asymptomatic and diabetes was incidentally detected during a routine checkup. Clinical and biochemical data and treatment following diagnosis was reported in table 1. In both patients, IR or surrogate markers of IR were detected.

The prevalence of diabetes was higher in prepubertal compared to pubertal subjects (p=0.03), similarly in males and females (p=0.8).

No association between metabolic alterations and type of nutritional support (p=0.1) or drug exposure was noted (p=0.9).

Table 2. Clinical and metabolic feature of the 2 patients with diabetes

	Patient 1	Patient 2
Sex	Male	Female
Age	4	8
Family history for diabetes	absent	absent
Neurological disorders	lissencephaly with cerebellar dysplasia	corpo callosum hypoplasia, delayed myelination, simplified gyration
Concomitant pathologies	none	biatrial enlargement
Treatment	anticonvulsive drugs	growth hormone
Ketoacidosis at diagnosis	absent	absent
Symptoms recorded at diagnosis	none	none
Glycemia at the diagnosis	355	490
HbA1c	7.8	9.5
Waist circumference (cm)	50 (<50 ^o centile)	48 (<50 ^o centile)
Waist-to-height ratio	0.45	0.44
BMI (kg/m²)	14.8	12.6
BMI z-score	1.5	-1.6
HOMA-IR	10.6	1.6
Triglyceride-glucose index	9.58	9.83
c-peptide	Not available	1.6
Autoimmune markers		
islet cell autoantibodies	Not available	Negative
autoantibodies to GAD (GAD65)	Negative	Negative
autoantibodies to the tyrosine phosphatases IA-2	Negative	Negative
autoantibodies to zinc transporter 8 (ZnT8)	Not available	Negative
HLA risk haplotypes	Not available	Absent
Therapy following diagnosis	Metformin	Insulin

Conclusions

In conclusion, T2D in NI children and adolescents could represent a new emerging entity in subjects without obesity. Insulin resistance and/or surrogate marker of insulin resistance index may be useful for the early screening of these at-risk disabled populations in order to prevent diabetes.