Metabolic alterations in patients affected by Pseudohypoparathyroidism 1A (PHP1A): preliminary data from single italian center

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Background

Pseudohypoparathyroidism (PHP) is a very rare disease characterized by hormone resistance due to defect of the α subunit of the stimulatory G protein (Gsα), its prevalence in Italy has been estimated in 1/150000. Hypocalcemia due to parathyroid hormone (PTH) resistance is common. PHP1A determined by maternal LoF mutations in GNAS, presents severe obesity as early feature with increased risk of developing metabolic derangement during life. Growth hormone deficiency, when present, decreased resting energy expenditure and MC4 receptor (MCR4) deregulation have been advocated as possible causes. To our Knowledge only very recent few and preliminary studies have addressed this topic in PHP1a .

Objective and hypotheses

We present preliminary data from database of patients followed in our center affected by PHP1A (clinical and genetically confirmed) with the aim of evaluating the metabolic alteration and possible relation with vitamin D, PTH and calcium

Patients and Methods

All subjects affected by genetically confirmed PHP1A were included. Auxological parameters (BMI; BMI SD), biochemical (calcium, phosphorus, ALP, metabolic (glycaemia, insulin basal and after OGTT in subjects with age>6 years, LDL, HDL, cholesterol, triglyceride, AST) and hormonal parameters (TSH, FT4, PTH, 25OHD) were collected and on the basis of fasting glucose and insulin values as previous reported ([HOMA-IR = (insulin0 (μIU/ml) x glucose0 (mmol/l))/22.5)]). Data were analyzed to find correlation also with ongoing therapies (vitamin D and hormonal replacement where present). As control group we used data from our database of healthy children not taking any therapy comparable for age, gender and BMISD. Statistical analysis was performed using SPSS package for Windows 17.0.

Results

To date 19 patients were included (mean age: 13.04±9.57 years; range: 3-20 years; 58% males) and 47 control patients (mean age: 12.78±2.48 years; range: 5-20 years; 51% males). Out of 19 PHP1A patients, 16 were on Calcitriol (1-25OH vitamin D3) and 15 on Levothyroxine. None were on sex steroid or GH therapy, hypolipidic or antihypertensive drugs. None of the control patients are taking any therapy affecting bone, metabolism or growth. None of PHP1A as well as control patients is affected by Metabolic Syndrome according to international criteria for children .

As expected no differences in age, BMISD and pubertal development was found between patients and control group, although 89% (=17) of PHP subjects and 96% (=45) of control subjects may be classified as Obese/overweight (BMISD>1.4). Statistically lower calcium and Phosphorus and higher PTH and 25OHD levels were found in PHP1A patients compared to control pairs (Table).

We did not find any statistically difference in all the biochemical metabolic parameters, insulin resistance index (HOMAIR), insulin and glycemia basal and after OGTT (n=8), HBA1c and blood pressure parameters between PHP1A and control group, except higher LDL values in PHP patients. In the PHP1A patients challenged with OGTT only 1/8 (12.5%) showed IGT comparable to 7 subjects in CNT (14.9%; p=0.661) Thyroid function is normal and comparable between groups (Table). Although with limit of sample size, we compared all the parameters between pts on (n.16) vs without (n.3) vitamin D and only age was statistically significant (6.3 yrs vs 18.1 yrs) (data not shown). Univariate analysis among all variables did not show any significant correlation in both groups except a negative correlation in PHP patients between 25OHD values and LDL values (r= -0.816; p=0.002).

	PHP1A (n=19)		CNT (n=47)		p
	median	IQR	mean	IQR	
ANTHROPOMETRIC PARAMETERS					
Gender (M/F)	11/8		24/23		0.740
Pubertal	42.11%	(8/19)	58.69%	(27/47)	0.279
Age (yrs)	10.20	16.90	11.90	11.50	0.860
BMI	23.30	20.50	28.30	24.50	0.014
BMISD	1.99	2.74	2.40	0.60	0.531
Waist/Height	0.61	0.00	0.60	0.26	0.834
SysBP (mmHg)	122.50	45.00	117.50	49.00	0.984
DyaBP (mmHg)	73.00	52.00	70.00	57.00	0.730
LABORATORY PARAMETERS					
Calcium (mg/dl)	9.50	4.00	9.90	3.00	0.003
phoshorus (mg/dl)	5.10	4.80	4.60	2.80	0.001
PTH (pg/ml)	219.00	1094.00	40.00	97.00	0.000
ALP (U/L)	482.00	890.00	569.00	1080.00	0.376
25OHD (ng/ml)	27.25	150.80	25.45	52.80	0.031
colesterol (mg/dl)	171.00	105.00	153.00	137.00	0.333
HDL (mg/dl)	38.50	43.00	41.00	55.00	0.953
LDL (mg/dl)	122.50	69.00	86.00	133.00	0.021
trygliceride (mg/dl)	76.00	196.00	90.00	177.00	0.884
GPT (U/l)	21.00	108.00	22.50	63.00	0.949
glycemia (mg/dl)	82.00	31.00	86.00	37.00	0.132
Glycemia 120' (mg/dl)	109.00	77.00	112.00	85.00	0.812
Insuline (mU/l)	17.74	59.43	20.48	50.50	0.453
Insuline 120' (mU/l)	167.30	148.80	111.00	112.80	0.797
HbA1c (mmol/mol)	34.00	6.00	35.00	15.00	0.521
HOMA-IR	3.45	10.80	4.70	12.90	0.316
TSH (mcU/ml)	2.40	6.27	2.33	21.53	0.488
FT4 (ng/dl)	1.29	1.21	1.16	0.96	0.093

Conclusion

In conclusion our data demonstrated in a pediatric population of PHP1A the presence of increased risk of overweight/obesity and absence of metabolic or glycemic alteration when compared to matched control peers.

Vitamin D and thyroxin therapy did not seem to influence metabolic parameters.

We recognize that these are preliminary data and at the moment recruitment of patients is ongoing in order to confirm these data on larger population stratified for gender, BMI and age, but very few is known on this interesting and debated topic.

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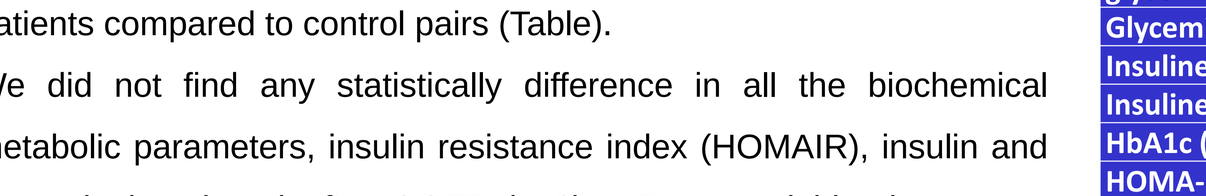

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