

# Acquired generalized lipodystrophy in a young lean Chinese girl

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## Abstract

Lipodystrophies is a really rare group of diseases characterized by altered body fat amount and/or repartition and serious insulin resistance. We reported a lean Chinese girl with acquired generalized lipodystrophy, who had a long history of poorly controlled diabetes mellitus (DM) despite with extremely high dose insulin (6 u/kg/d) therapy, combined with severe hypertriglyceridemia and acanthosis nigricans. The differential diagnosis of Lipodystrophies should be considered in lean patients presenting with early onset DM, combined with serious insulin resistance.

## INTRODUCTION

Lipodystrophies is a really rare group of diseases (1 to 12 million) characterized by altered body fat amount and/or repartition and serious insulin resistance (Oral *et al.* 2002). In this article, we reported a lean Chinese girl with Acquired generalized lipodystrophy (AGL, known as Lawrence syndrome). This patient had a 10 year history of poorly controlled DM despite with high dose insulin therapy (6 u/kg/d), and extreme hypertriglyceridaemia.

## CASE REPORT

This only child of the parents was born after 38 weeks gestation, with low birth weight (2.1 kg). Since onset puberty at age of 9 years, she was noticed to have a generalized and progressive loss of sc fat and acanthosis nigricans. At the age of 13, she was incidentally detected to have serious hyperglycemia (fasting blood glucose 9.0 mmol/l, HbA1c 12.0%) and hypertriglyceridemia

(15.9 mmol/l). Then she was diagnosed to have DM and initially treated with insulin pump. But the blood glucose was badly controlled even with high dose of insulin. Because of poorly controlled hyperglycemia, Her vision loss became serious and ophthalmoscopy showed diabetic retinopathy (Stage VI) at the age of 20 years.

Her height was 154 cm and weight was 35 kg respectively (BMI 14.0 kg/m<sup>2</sup>). The patient presented with a generalize atrophy of the sc fat in extremities, face and trunk. Acanthosis nigricans was present in the axillary and nuchal folds. The cardiovascular and respiratory examinations were unremarkable.

The fasting and postprandial insulin concentrations reached 54.7 mmol/l and 77.4 mmol/l respectively under no insulin injection condition. HbA1c was 10.7%. Thyroglobulin antibody and thyroid peroxidase antibody, as well as antinuclear antibody were all in normal range.

Hyperinsulinaemic-euglycaemic clamp showed the glucose infusion rate was 0.54 mg/kg/min

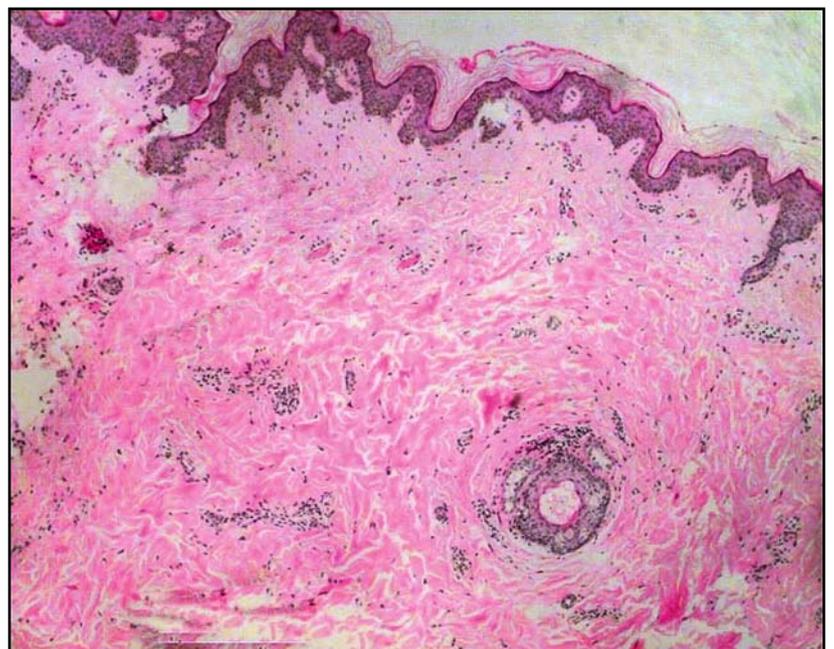


**Fig. 1.** T-1 weighted magnetic resonance imaging revealed the absence of body fat at both sc in extremities (a,b) and visceral levels (c).

(normal range  $11.56 \pm 1.74$  mg/kg/min), which further confirmed her serious insulin resistance. Two important adipokins, leptin and adiponectin were both at extremely low level ( $0.273$   $\mu$ g/l, normal range  $0.22 \pm 0.14$   $\mu$ g/l) and adiponectin ( $0.12$  mg/l, normal range  $2.6 \pm 0.6$  mg/l) were detected, which is consistent with the endocrinological features of GL.

Magnetic resonance imaging revealed the absence of body fat at both sc in extremities and visceral levels (Figure 1). A deep skin and muscle biopsy at deltoid muscle were performed. Histological examination reviewed obvious fat loss of sc, which confirmed the diagnosis of GL (Figure 2). Four special genes (LAMN, PPARG, AGPT2, and Sepin) responsible for congenital Lipodystrophies were detected. As we predicted, no gene mutation were identified in all the exons. So the presumptive diagnosis of AGL was finally confirmed.

As for this patient, the best therapy was human recombination leptin. Unfortunately, it was unavailable for



**Fig. 2.** Histological examination of skin biopsy at deltoid muscle reviewed obvious fat loss of sc, and confirmed the diagnosis of GL.

her. So the routine combination therapy with insulin pump (150 u/d), metformin 0.5 tid and pioglitazone 30 mg qd were administrated. But the blood glucose was still suboptimal controlled.

## DISCUSSION

When fat depots reduce because of lipodystrophy, TG present on circulating lipoproteins, chylomicrons and VLDL, can only be partially stored in fat depots. This will lead to increased circulating TG. Reduced fat amounts result in reduced circulating leptin and adiponectin levels, causing extremely insulin resistance (Lakhdar *et al.* 2013).

Lipodystrophy is a heterogeneous condition characterized by an inherited or acquired deficiency, generalized or partial deficiency. These disorders are generally associated with severe insulin resistance.

CGL is one subtype with apparent near complete absence of adipose tissue at birth or in early infancy. The pattern of body fat loss is near total absence of metabolically active adipose tissue, however preservation of mechanical fat. Mutations in two responsible genes (BSCL2 and AGPAT2) are most frequently reported. Familial partial lipodystrophy of the Dunnigan type (FPLD), dominantly inherited, and is characterized by a lack of adipose tissue in the limbs, buttocks and trunk with fat accumulation in the neck and face. It results from mutations in genes encoding the nuclear protein lamin A/C (LMNA) or the adipose transcription factor peroxisome proliferator-activated receptor (PPAR $\gamma$ ) (Kozusko *et al.* 2015).

The term acquired lipodystrophy (AL) is used for patients who clearly don't have an inherited form of lipodystrophy by clinical history. AGL is commonly associated with panniculitis and autoimmune disorders such as juvenile dermatomyositis, but most often is idiopathic. The onset of sc fat loss in patients with AGL occurs usually during childhood, and most of them have generalized loss of fat. It has been hypothesized that AGL represents an autoimmune disorder because it has been associated with other autoimmune diseases. Patients with acquired partial lipodystrophy (APL) always show a gradual onset of bilaterally symmetrical loss of subcutaneous fat from the face, neck, upper extremities and abdomen sparing the lower extremities (Garg 2011).

Since the extremely low prevalence of AGL, the definite diagnosis is usually hard to make. As for our patient, she was noticed to have hyperglycemia for 10 years, badly controlled even with high dose insulin. Subsequently, some important experimental evidences indicated the diagnosis of AGL. The first is leptin and adiponectin deficiency. The second is obvious fat loss in sc and sat in MRI, which was confirmed with skin and muscle biopsy. All the common 4 genes caus-

ative of CGL and FPLD had no mutation. No other autoimmune disease present and no organ specific autoimmune antibodies were detected. Altogether, the diagnosis of idiopathic AGL was definitely made, which had been delayed for 10 years since the onset of extremely insulin resistance.

To this special disease, it is hard to get hyperglycemia well controlled with routine common insulin sensitizers (metformin and/or TZD) or/and even high doses of insulin. Human recombinant leptin has been administered for GL in some clinical trials (Muniyappa *et al.* 2014; Ebihara *et al.* 2007). The results showed it can improve both insulin sensitivity and insulin secretion dramatically, resulting in rapidly improvement in glucose metabolism and substantial reductions of the triglyceride level. Such effects can maintain for up to 36 months. These rapid and powerful effects are associated with a marked reduction in intrahepatic and intramyocellular lipid content.

## CONCLUSION

The diagnosis of GL is usually delayed for long time because of its really lower prevalence, atypical presentation and various phenotypes. This disease should be considered in differential diagnosis of lean patients presenting with early onset DM, combined with severe hypertriglyceridemia, hepatosplenomegaly and/or hepatic steatosis, acanthosis nigricans (Ovalle 2010).

### Conflict of interest statement

The authors have no conflict of interest to declare.

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# The first description of metyrapone use in severe Cushing Syndrome due to ectopic ACTH secretion in an infant with immature sacrococcygeal teratoma

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## Abstract

Cushing syndrome due to ectopic secretion of ACTH in infants is rare. The treatment of choice is radical resection of the tumour in combination with pre-operative chemotherapy using steroidogenesis inhibitors if necessary. If radical surgery is not possible, palliative treatment of hypercortisolemia is recommended. The most frequently used drug in infants is ketoconazole. Experience with the use of metyrapone is poor. We report an 8-month-old female infant with congenital immature sacrococcygeal teratoma secreting AFP, beta hCG and ACTH who had undergone non-radical resection of the tumour mass and was receiving standard risk chemotherapy (vinblastine, bleomycin, and cisplatin). The infant initially presented at the age of 6 months with ACTH-dependent Cushing syndrome (cortisol and ACTH level 325 ng/mL, 112 pg/mL respectively). Treatment with ketoconazole was initiated with a dose of 600 mg/day. Due to its ineffectiveness metyrapone was added in increasing dosages, up to 1,500 mg/day. In addition the schema of chemotherapy was changed (adriamycin, bleomycin, carboplatin), which resulted in normalization of cortisol levels and blood pressure. There were no metyrapone side effects during the treatment period. We can conclude that treatment with metyrapone at a dose of 1500 mg/day might be effective and safe in infants with Cushing syndrome.

## INTRODUCTION

Cushing syndrome (CS) due to ectopic secretion of ACTH in infants is extremely rare and challenging to treat. The treatment of choice is radical resection of the ACTH secreting tumour with pre-operative pharmacological inhibition of steroidogenesis and chemotherapy if neces-

sary. If radical surgery is not possible, palliative treatment of hypercortisolemia is recommended. Inhibitors of steroidogenesis are difficult to use in this age group because data regarding effective dosage regimens is poor and there is no evidence of long-term safety and efficacy (Traina *et al.* 2013; Salunke *et al.* 2010). The most frequently used agent is ketoconazole. Experience with the use

of metyrapone in that age group is poor (Garge *et al.* 2013). We report a case of a female infant with severe Cushing syndrome due to ectopic ACTH secretion by an immature sacrococcygeal teratoma. This is the first description of metyrapone use in severe CS due to ectopic ACTH secretion in an infant.

## CASE REPORT

A 8-month-old female infant was referred to the endocrinologist due to ACTH dependent CS. The patient was born at term to a G2 P2 mother by cesarean section with a birth weight of 4,280 g. The physical examine revealed anal atresia and a large tumour mass in the sacrococcygeal and pelvic region. Additional laboratory testing in the first days of life revealed a significant increase in alfafetoprotein (AFP) levels (59,000 ng/mL). At the age of 1 week, non radical resection of the tumor and the implantation of a colostomy were performed. The histopathological examination revealed a grade 3 immature teratoma. After surgery AFP levels returned to normal but a CT scan confirmed residual tumour mass (27×21×28 mm).

At the age of two months an increase in AFP and beta human chorionic gonadotropin (bata HCG) (379.5 ng/mL and 192 IU/L respectively) accompanied by an increase in tumour mass were found. Standard risk chemotherapy VBP (vinblastine, bleomycin, and cisplatin) was introduced. After 3 blocks of chemotherapy there was no regression in tumor mass diameters. At the age of 4 months a rapid increase in appetite and subsequent body weight were noticed accompanied by a systematic increase in blood pressure.

At the age of 6 months blood tests revealed elevated levels of cortisol and ACTH (325 ng/mL, 112 pg/mL respectively). The schema of chemotherapy was upgraded to high risk VIP (high risk etosposid, ifosamid, cisplatin), but there was still no regression in tumor mass and cortisol levels were increasing gradually up to 627 ng/mL. Ketoconazole was introduced at the initial daily dose of 400 mg. Despite intensive hypertensive treatment (metoprolol, captopril, aldacton), blood pressure was continuously increasing. The patient developed a hypertensive crisis with seizures and blood pressure at a maximum value of 210/160 mmHg.

On admission to the Children's University Hospital in Kraków at the age of 8 months, she presented in good general condition, with a body weight of 9 kg and blood pressure of 120/70 mmHg. Blood cortisol levels were high (739.8 ng/mL). The dosage of ketoconazole was increased to 600 mg without any significant effect on cortisol levels (699 ng/mL). At this point we decided to introduce metyrapone (125 mg twice a day). After 4 days of treatment, cortisol levels returned to within the normal range (172 ng/mL). After four days of stability, a rapid increase in cortisol levels up to 700 ng/mL was found. Metyrapone was gradually increased to the maximum dose of 250 mg every 4 hours (1,500 mg per day).

In addition, second line chemotherapy was introduced (ABK protocol: adriamycin, bleomycin, carboplatin). After 4 days of such treatment cortisol levels decreased to 132 ng/mL and remained stable. Appetite decreased as well and there was no increase in body weight. Blood pressure was normal (90/57 mmHg). During the whole treatment period we did not observe any metyrapone side effects.

## DISCUSSION

Ectopic secretion of ACTH by an immature teratoma is rare. There is one description of ACTH dependent CS due to immature sacrococcygeal teratoma in an adult female and one due to congenital immature teratoma in the region of the pituitary gland in an infant (Salunke *et al.* 2010; Moreno-Fernández *et al.* 2008). In the second case hypercortisolemia was successfully treated with ketoconazole at a dose of 200mg/day prior to the surgery (Salunke *et al.* 2010). On the contrary in this case a dose of 600 mg/day was not effective in the treatment of hypercortisolemia.

For this reason we decided to use metyrapone as second line therapy. Metyrapone is an inhibitor of endogenous adrenal corticosteroid synthesis. It inhibits the enzyme responsible for the 11 $\beta$ -hydroxylation stage in the biosynthesis of cortisol and to a lesser extent, aldosterone. The major potential side effects reported in adult patients are hirsutism, acne and mineralocorticoid effects (hypertension, hypokalemia and edema) (Feelders *et al.* 2010).

An additional problem in pediatric patients is the dosage, because commercially available capsules contain 250 mg of metyrapone and are not divisible. Metyrapone is occasionally used for short-term treatment of CS prior to surgery. Its efficacy in adults in the reduction of cortisol levels is about 75% (Traina *et al.* 2013; Feelders *et al.* 2010).

Ketoconazole is an antifungal agent that, in higher dosages, reduces adrenal steroid production via inhibition of multiple steroidogenic enzymes. Data from retrospective studies in adults show, that ketoconazole in a dose range between 400 and 1,200 mg/day can decrease cortisol production in about 70% of patients with CS (Feelders *et al.* 2010).

There is no data regarding the efficacy of these this drug in infants, however it is the most frequently used inhibitor of steroidogenesis in this age group (Dutta *et al.* 2012) In the presented case the dose of 250 mg/day was initially effective, but after a short amount of time, cortisol levels increased and an increase of the dose up to 1,500 mg/day was needed.

In addition second line chemotherapy was introduced as well (ABK protocol adriamycin, bleomycin, carboplatin). The result was a decrease in cortisol levels to 94.2 ng/mL This is the first description of metyrapone treatment in an infant with CS due to ectopic secretion of ACTH. During the whole treatment period with

increasing doses of metyrapone (up to 1,500 mg daily) and regular monitoring of cortisol levels and blood pressure, no side effects of the drug were observed.

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