

CASE REPORT

Hyperandrogenism as a clinical manifestation of familial partial lipodystrophy type 2 in an adolescent female patient

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ABSTRACT

We present a case report of a girl with significant hyperandrogenism with accompanying metabolic disorders. In the physical examination, attention was drawn to tall stature, excessive body mass with a muscular build, broad shoulders and a narrow pelvis, low timbre of voice, acne lesions, enlarged mandible, hirsutism (19 points on the Ferriman-Gallwey scale), and elevated blood pressure. Substantial hyperandrogenemia was noted, with a significantly increased testosterone level and elevated levels of adrenal androgens. Based on steroid metabolome analysis from 24-hour urine collection, congenital adrenal hyperplasia was ruled out. Dyslipidemia and impaired glucose tolerance with hyperinsulinism in the oral glucose tolerance test were found. Magnetic resonance imaging of the abdomen and pelvis revealed a fatty liver and overgrowth of muscles and mesentery with adipose tissue. Whole exome sequencing was performed, revealing the presence of a known, pathogenic molecular variant, c.1394G > A, in the *LMNA* gene, associated with the occurrence of familial partial lipodystrophy.

KEY WORDS:

dyslipidemia, hyperandrogenism, lipodystrophy, familial partial lipodystrophy, carbohydrate disorders.

INTRODUCTION

Hyperandrogenism is defined by clinical features or biochemical results of increased androgen concentration. The most common symptom of hyperandrogenism in women is hirsutism [1]; other symptoms include acne, alopecia with male pattern of hair loss and oligo- or amenorrhea [2]. Hyperandrogenism prevalence in adolescents is estimated at 3–20% [3, 4]. The most common etiology of hyperandrogenism in prepubertal girls is premature adrenarche (60%), followed by congenital adrenal hyperplasia (4%). In the pubertal period, polycystic ovary syndrome (PCOS) dominates (20–40%). Androgen-secreting tumors are rare (0.2%); however, features of virilization in adolescent girls such as enlargement of the clitoris, in-

creased muscularity, deepening of the voice, severe cystic acne or seborrhea, rapid progression of pubic hair or hirsutism demand a thorough investigation [5].

We present a case report of a girl with significant hyperandrogenism with accompanying metabolic disorders.

CASE REPORT

A 13-year-old patient identifying as female was admitted to the Department of Pediatrics and Pediatric Endocrinology for the diagnosis of hyperandrogenism. In the medical history, the patient reported excessive body hair and acne lesions on the skin of the face and back for several years. In the family history, the mother and maternal grandmother have features of hyperandrogenism

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FIGURE 1. Muscular body build of the patient's mother

and muscular physique (Figure 1). In the physical examination, attention was drawn to tall stature (170.6 cm, 90–97th percentile, hSDS = 1.7), excessive body mass (75 kg, BMI > 97 c, Z-score BMI IOTF = 1.83), with a muscular build, male body shape with broad shoulders and a narrow pelvis (Figure 2), low timbre of voice, acne lesions on the skin of the face and back, enlarged mandible, hirsutism (19 points on the Ferriman-Gallwey scale) and elevated blood pressure (ranges 116–158/69–93 mm Hg). No other abnormalities were observed on physical examination. The degree of puberty was P5 B3 according to the Tanner scale. The external genitalia were typically female.

Hormonal tests showed a normal daily cortisol profile, normoprolactinemia, euthyroidism, and an age- and gender-appropriate level of estradiol, while we observed an elevated luteinizing hormone/follicle stimulating hormone ratio [5, 6]. Sex hormone-binding globulin, anti-Müllerian hormone and leptin levels were within the normal range, with leptin at the lower limit. Substantial hyperandrogenemia was noted, with a significantly increased testosterone level and elevated levels of adrenal androgens: DHEA-S, androstenedione and 17-OH-progesterone (Table 1). Based on steroid metabolome analysis from 24-hour urine collection, congenital adrenal hyperplasia was ruled out. However, significantly elevated excretion of androgen metabolites, elevated excretion of 17-OH-P metabolites (of ovarian-adrenal origin) and elevated production of corticosteroids with normal metabolism (according to body weight) were found (Table 2). In addition, dyslipidemia, impaired glucose tolerance, and hyperinsulinism in the oral glucose tolerance test were found (Table 1). Other basic biochemical tests showed no abnormalities. The karyotype determination revealed 46,XX karyotype.

Abdominal and pelvic ultrasonography showed signs of fatty liver and asymmetry of ovaries – the right one



FIGURE 2. The patient's triangular silhouette

with a volume of 3.5 ml and the left one with a volume of 6.0 ml. Magnetic resonance imaging of the abdomen and small pelvis revealed a fatty liver and visible overgrowth of all available muscles and mesentery with adipose tissue. The volume of the ovaries was quite large for a girl who was not yet menstruating. Bone age was evaluated at 17 years according to the Greulich-Pyle atlas. We performed evaluation of body composition using electrical bioimpedance, finding that fat-free mass was 76% of whole body mass, of which muscle mass was 72%, while body fat was 24%, which was within the normal range for girls aged 13. The distribution of fat tissue involved mainly the limbs (about 30%), while the distribution on the torso was about 15%.

Due to elevated blood pressure, Holter RR was performed, confirming elevated blood pressure. The consulting cardiologist did not confirm any heart or aorta defect. Antihypertensive treatment with an angiotensin converting enzyme inhibitor was recommended.

Dietary and psychological consultations were carried out. The principles of the diet in hypercholesterolemia, with the restriction of easily digestible carbohydrates, were presented to the patient. Psychological support was recommended. Due to hyperinsulinism, metformin 3 × 500 mg was added to the treatment. Initially, a spironolactone preparation in the dose of 25 mg was used in the treatment of hirsutism, then a preparation containing estrogen and progestin was added to the treatment. After 4 months of treatment, including after 1 month of use

of the combination preparation, menarche occurred. Thanks to the treatment and the use of aesthetic medicine methods, the patient currently shows no hirsutism during physical examination.

The patient is under the care of the Endocrinological Clinic. The results after a few months of antiandrogen have been normalized. However, metabolic parameters are still abnormal (Table 3).

Based on the overall clinical presentation, the girl was referred for further diagnostics at the Genetic Clinic. Firstly, the test for congenital generalized lipodystrophy (Berardinelli-Seip syndrome) was performed, with a negative result. Then whole exome sequencing was performed revealing the presence of a known, pathogenic molecular variant c.1394G > A p. (Gly465Asp) in the *LMNA* gene, correlated with the occurrence of familial partial lipodystrophy (FPLD), type 2; OMIM#151660; ORPHA: 2348.

In order to determine the origin of the above-mentioned molecular variant and to determine the risk of the disease occurring in other family members, it is necessary to perform carrier tests for the detected change in the patient's biological parents – especially as the mother of the patient was diagnosed with hypertension during her third pregnancy (the next child after our patient), has problems with hypercholesterolemia, and also has a very muscular body. Additionally, the grandmother on the mother's side also had a muscular build, and from the medical history we found out that she died at the age of 54 due to a heart attack.

While waiting for the review of this article, genetic tests were performed to determine the presence of the mentioned variant in the *LMNA* gene in the patient's parents and brother. Sequence analysis confirmed the presence of the same variant in the patient's mother and brother, while the variant was not detected in the father. The father was asymptomatic, while the patient's brother was diagnosed with hypercholesterolemia.

DISCUSSION

The patient exhibits severe hirsutism, as evidenced by the score on the Ferriman-Gallwey scale. Additionally, the occurrence of acne, a lowered voice timbre, and male-type muscularity necessitates a particularly thorough diagnosis. Whole exome sequencing was performed, revealing the presence of a known, pathogenic molecular variant in the *LMNA* gene. However, taking into consideration the overall history, physical examination, and results of additional tests, our differential diagnosis included a virilizing ovarian tumor, observation for PCOS, and congenital forms of lipodystrophy.

Androgen-secreting tumors are rare, but, taking into account our patient's clinical features of lowered voice timbre, increased muscularity, and a testosterone level above 150–200 ng/dl, it should be considered. Repeat

TABLE 1. Biochemical and hormonal profile of the patient

Parameters	Value	Standard range
TCh [mg/dl]	243	114–190
TG [mg/dl]	223	< 150
LDL [mg/dl]	150.4	68.0–70.0
HDL [mg/dl]	48	37.0–70.0
GLC 0 [mg/dl]	85	70–99
GLC 120 [mg/dl]	172	< 140
INS 0 [μU/ml]	51.7	6–29.1
INS 120 [μU/ml]	> 300	< 60
HOMA-IR	10.7	< 2.5
HbA1c (%)	5.7	4–6
COR 8:00 [ug/dl]	18.6	7.0–25.0
COR 24:00 [ug/dl]	3.28	2.0–9.0
PRL [mIU/l]	445	80.6–467.7
TSH [uU/ml]	2.54	0.4–5.0
ft4 [ng/ml]	1.27	0.6–1.4
E2 [pmol/l]	173.8	Follicular: 45.4–854.0 Luteal: 81.9–1251.0
LH [IU/l]	26.7	Follicular: 0.2–26 Ovulation: 25–57
FSH [IU/l]	4.79	Follicular: 1.4–9.6 Ovulation: 2.3–21
SHBG [nmol/l]	15.15	19.8–155.2
AMH [ng/ml]	5.63	4.0–21
Leptin [ng/ml]	3.99	3.7–11.1
TTE [ng/ml]	241.8	10–40
DHEA-S [ug/dl]	367	25.2–213.9
Androstenedione [ng/ml]	5.57	Follicular: 0.75–3.10 Luteal: 0.94–3.20
17-OHP [ng/ml]	2.23	Follicular: 0.13–0.89 Luteal: 0.16–2.05

17-OHP – 17-hydroxyprogesterone, AMH – anti-Müllerian hormone, COR – cortisol, DHEA-S – dehydroepiandrosterone, E2 – estradiol, FSH – follicle stimulating hormone, GLC – glucose, HbA_{1c} – glycated hemoglobin, INS – insulin, LDL – low-density lipoprotein cholesterol, LH – luteinizing hormone, PRL – prolactin, SHBG – sex hormone binding globulin, TCh – total cholesterol, TG – triglycerides, HDL – HDL cholesterol, TSH – thyroid stimulating hormone, ft4: free T4, TTE – testosterone

androgen measurements may be required with suspicion of tumor, while imaging should be proposed to patients with a high index of tumor suspicion based on clinical and biochemical data [5].

The most commonly used definition of PCOS is based on the Rotterdam consensus criteria (2003) (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004) [6]. However, these diagnostic criteria in adolescents are controversial, as pathological features observed in adult women can be physiological in adolescents [7, 8]. The diagnosis of PCOS should not be established in the first years after menarche. Most researchers agree that we should wait at least two years from menarche [9–11]. Although obesity and insulin resistance

TABLE 2. Results from steroid metabolome from 24-hour urine collection

Parameters	Result [µg/24 h]	Reference range
Androsterone	3956.0	710–3140
Etiocholanolone	1316.8	380–2590
11-ketoandrosterone/etiocholanolone	495.2	–
11-hydroxyandrosterone	1445.3	180–912
11-hydroxyetiocholanolone	912.6	54–750
Dehydroepiandrosterone	901.8	73–559
5-androstenediol	709.7	130–610
16α-hydroxy-DHA	2939.8	50–490
5-androstenetriol	709.7	130–610
5-pregnanetriol	1061.1	80–390
16α-hydroxy-pregnenolone	0.0	–
17-hydroxy-pregnanolone	436.9	25–208
Pregnanetriol	1286.0	185–885
Pregnanetriolone	31.1	10–50
Pregnanediol	231.3	< 900
Estrone	9.4	0–52
Estradiol	2.5	0–15
Estriol	19.8	1–30
Tetrahydro-11-deoxycortisol	164.4	20–72
Tetrahydro-11-deoxycorticosterone	12.6	< 16
Tetrahydro-11-dehydrocorticosterone	494.2	–
Tetrahydro-corticosterone	183.4	20–256
Allo-tetrahydro-corticosterone	512.7	78–543
Tetrahydro-aldoosterone	47.3	7–51
Tetra-hydrocortisone	7123.0	585–3960
Tetra-hydrocortisol	3159.0	315–2060
Allo-tetrahydrocortisol	4792.3	420–2660
α-cortolone	2412.6	360–1420
β-cortolone	1333.2	75–925
β-cortol	679.7	30–800
α-cortol	777.4	60–300
Free cortisone	312.9	17–115
Free cortisol	139.1	9–52
Free cortisol/free cortisone	0.4	0.35–0.75

TABLE 3. Biochemical profile of the patient during metformin treatment

Parameters	Value	Standard range
TTE [ng/dl]	30.82	10–40
GLC 0 [mg/dl]	118	70–99
INS 0 µU/ml	86.1	6–29.1
HOMA-IR	25.06	< 2.5

GLC – glucose, INS – insulin, TTE – testosterone

are common in adolescent girls with hyperandrogenism, they should not be used to diagnose PCOS among adolescent girls [12]. The etiology of PCOS remains unclear. The current state of knowledge suggests mainly a genetic, polygenic background of the disorders. Vink *et al.* studied the heritability of PCOS in a Dutch population, concluding that the influence of genetic factors on the pathogenesis of PCOS is significant [13].

Another considered diagnosis was congenital familial lipodystrophy. A known, pathogenic molecular variant, c.1394G > A p. (Gly465Asp), in the *LMNA* gene was found, correlated with the occurrence of FPLD type 2 (FPLD2, Dunnigan type). It is the most common type of FPLD caused by changes in the lamin A/C (*LMNA*) gene. The reduced number of fat cells may be connected with altered interaction of the lamina with chromatin, which leads to altered cell division and possibly increased apoptosis of cells. Mutations in the *LMNA* gene have also been reported in several other diseases, such as dilated cardiomyopathy and various forms of muscular dystrophy [14]. Variant c.1394G > A has been described previously [15–17]. Familial partial lipodystrophy type 2 typically presents during puberty with regional loss of subcutaneous fat from the extremities, buttocks, and trunk, with accumulation of fat in the face and neck (cushingoid face). An increase in muscle mass is observed. Metabolic complications appear gradually during adolescence or adulthood and include insulin resistance, high blood pressure (both observed in our patient), diabetes, fatty liver disease, acanthosis nigricans, and premature atherosclerosis, with an increased risk of coronary heart disease. Some patients may experience symptoms of PCOS such as hirsutism, oligomenorrhea, and infertility. Other symptoms may include recurrent acute pancreatitis and steatohepatitis [18].

Recommendations for the further care of patients with FPLD2 include monitoring the activity of liver enzymes and periodically performing liver ultrasound examinations. Cardiovascular examinations are necessary to detect rhythm and conduction disorders and early atherosclerosis. Reduced intake of fats and carbohydrates in the diet (~50–60% carbohydrates, 20–30% fat, and 20% protein) and daily physical activity are very important [19]. However, the patient should be supervised by a cardiologist due to the risk of heart rhythm disturbances that may occur due to changes in the *LMNA* gene. Depending on the test results, pharmacological treatment should include the use of metformin and lipid-lowering drugs. In the further stage of treatment, glucagon-like peptide 1 receptor agonists should be considered to improve glycemic control and reduce insulin requirements. The sodium-glucose co-transporter 2 inhibitors also have a beneficial effect on glucose control and cardiovascular and renal disease in type 2 diabetes mellitus so can be taken into consideration. Treatment of hypertriglyceridemia can be demanding and requires the combination of diet and fibrates as well as long-chain omega-3 fatty acids [20]. Metreleptin,

a leptin analogue, is recommended in Europe for the treatment of metabolic complications of partial lipodystrophy in adults and children over 12 years of age when standard treatment has not worked. Metreleptin therapy is based on daily injections. It improves the metabolic complications associated with lipodystrophy, which are partly related to adipocyte hormone deficiency. However, the costs of metreleptin are very high and are not covered by insurance. Its efficacy and the patient's tolerance together with compliance with therapy should be re-evaluated every 3–6 months. The beneficial effect of metreleptin treatment on fertility in FPLD2 patients has not been evaluated. The use of ethinyl estradiol in FPLD2 should be avoided in women with FPLD2 [21, 22].

CONCLUSIONS

In our patient, diet, metformin, an angiotensin converting enzyme inhibitor, spironolactone, and a preparation containing estrogen and progestin were used. We observed a reduction of the severity of hirsutism and achievement of regular menstruation, but with no effect on metabolic parameters. We are considering changing the sex hormone preparation as ethinyl estradiol is not recommended – especially as we observed metabolic complications in earlier generations, as the mother has hypertension and hypercholesterolemia, and the grandmother died at quite a young age from cardiological causes. Because of the result of molecular diagnostics, the use of metreleptin is being considered.

DISCLOSURES

1. Institutional review board statement: Not applicable.
2. We would like to thank the patient's mother for providing a photo of her figure as well as the patient and her parents for consenting to the photo.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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