Generalized lipodystrophy is a rare, complex, and clinically heterogeneous disorder characterized by the widespread lack or loss of subcutaneous adipose tissue in most or all parts of the body, and the associated loss of endocrine function, resulting in relative leptin deficiency.\textsuperscript{1,2}

**WIDESPREAD LACK OR LOSS OF ADIPOSE TISSUE\textsuperscript{1}**

**AND**

**METABOLIC ABNORMALITIES SUCH AS\textsuperscript{1}:**

- DIABETES MELLITUS REQUIRING HIGH DOSES OF INSULIN (U-500)
- HYPERTRIGLYCERIDEMIA: $\geq 500 \text{ MG/DL}$
- INSULIN RESISTANCE
- HYPERPHAGIA

**COULD IT BE GENERALIZED LIPODYSTROPHY?**
Relative leptin deficiency is a key pathogenic mechanism underlying severe and treatment-refractory metabolic disease in patients with generalized lipodystrophy.

In normal physiology, leptin acts in the brain and periphery to regulate energy homeostasis and metabolic function in the body:

- Decreases glucose synthesis and increases glucose uptake in skeletal muscle
- Prevents the accumulation of lipids in nonadipose tissues such as the liver and muscles
- Protects peripheral tissues from fat-induced toxicity by stimulating the breakdown of fatty acids
- Regulates food intake through a complex neural circuit in the hypothalamus

Serum leptin levels are typically low in patients with generalized lipodystrophy. However, leptin levels may not be a reliable indicator for diagnosis because:

- Levels vary depending on gender, BMI, age, and metabolic abnormalities
- Leptin assays have not been standardized
- Normative ranges of leptin have not been well established
In addition to the metabolic complications that individuals with generalized lipodystrophy face, they may also experience psychological distress due to abnormal physical appearance caused by their generalized lipodystrophy.\textsuperscript{6,16,17}

**METABOLIC ABNORMALITIES CAUSED BY RELATIVE LEPTIN DEFICIENCY MAY LEAD TO SERIOUS COMORBIDITIES\textsuperscript{1,14}**

Disease complications may vary among individuals with generalized lipodystrophy. Not all individuals will experience the same complications.\textsuperscript{1}

**METABOLIC ABNORMALITIES → SERIOUS COMORBIDITIES**

**METABOLIC ABNORMALITIES**

- Hyperphagia\textsuperscript{1}
- Hepatic steatosis\textsuperscript{1}
- Hypertriglyceridemia\textsuperscript{1}
- Insulin resistance and diabetes\textsuperscript{1}
- Proteinuric nephropathies\textsuperscript{14}

**SERIOUS COMORBIDITIES**

- Cardiovascular disease and heart failure\textsuperscript{1,15}
- Cirrhosis and liver failure\textsuperscript{1}
- Acute pancreatitis\textsuperscript{1}
- Kidney disease and renal failure\textsuperscript{6,15}
CONGENITAL GENERALIZED LIPODYSTROPHY (CGL)

CGL is an autosomal recessive disorder characterized by a generalized lack of adipose tissue at birth or shortly thereafter (within the first year of life), and is accompanied by prominent muscularity and subcutaneous veins.\(^1\)

<table>
<thead>
<tr>
<th>ALSO KNOWN AS</th>
<th>Berardinelli-Seip syndrome(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE OF ONSET</td>
<td>At birth or shortly thereafter(^1)</td>
</tr>
<tr>
<td>TYPICAL PRESENTING FEATURES</td>
<td>Generalized lack of fat with muscular appearance and acromegaloïd features and umbilical hernia(^1)</td>
</tr>
<tr>
<td>SUBCUTANEOUS FAT LOSS AREAS</td>
<td>Generalized, with near total lack of fat(^1)</td>
</tr>
<tr>
<td>SPARING FAT LOSS OR EXCESS FAT AREAS</td>
<td>None(^1)</td>
</tr>
<tr>
<td>METABOLIC ABNORMALITIES</td>
<td>Diabetes mellitus, insulin resistance, hypertriglyceridemia(^1)</td>
</tr>
<tr>
<td>CAUSE</td>
<td>Genetic(^1)</td>
</tr>
<tr>
<td>FEMALE-SPECIFIC FEATURES</td>
<td>Polycystic ovary syndrome, infertility(^1)</td>
</tr>
</tbody>
</table>

**OTHER FEATURES**
- Advanced bone age\(^6\)
- Mild mental retardation\(^2\)
- Accelerated growth in early childhood\(^6\)
- Hypertrophic cardiomyopathy\(^6\)
- Hepatosplenomegaly\(^6\)
- Acanthosis nigricans\(^6\)
- Hyperphagia\(^6\)
- Proteinuric nephropathies\(^14\)

**Consequences**

Common complications at birth or shortly thereafter include insulin resistance, elevated triglycerides, hyperphagia, and hepatomegaly. Metabolic abnormalities such as diabetes mellitus and hypertriglyceridemia can develop in infancy or adolescence.\(^1,17,18\)

The features of CGL are present at birth or shortly thereafter—much earlier than other types of lipodystrophy.\(^1\)

A Lateral view of an 8-year-old African-American female with CGL, type 1, due to homozygous c.377insT (p.Pro128AlafsX19) mutation in AGPAT2. The patient had generalized loss of subcutaneous fat with mild acanthosis nigricans in the axillae and neck. She had umbilical prominence and acromegaloïd features (enlarged mandible, hands, and feet).\(^17\)

B One-year-old female of African origin with CGL. Marked generalized loss of subcutaneous fat and striking muscularity is evident. The patient has umbilical prominence and slightly enlarged hands, feet, and mandible, which are suggestive of acromegaloïd features. The patient developed severe acanthosis nigricans, insulin-resistant diabetes mellitus, and severe hypertriglyceridemia by the age of 16 years. She had compound heterozygous mutations in the AGPAT2 gene (IVS4 -2A → G and 683 T → C mutations at the nucleotide level causing Gln196fsX228 and Leu228Pro changes at the protein level).\(^19\)
ACQUIRED GENERALIZED LIPODYSTROPHY (AGL)

AGL is characterized by a generalized loss of adipose tissue. In contrast to CGL, patients with AGL are born with normal fat distribution but lose fat in a generalized fashion over time, typically starting in childhood or adolescence.\(^1\)

<table>
<thead>
<tr>
<th><strong>ALSO KNOWN AS</strong></th>
<th>Lawrence syndrome(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE OF ONSET</strong></td>
<td>Childhood or adolescence(^2)</td>
</tr>
<tr>
<td><strong>TYPICAL PRESENTING FEATURES</strong></td>
<td>Extensive generalized fat loss that is usually insidious (over years) but can sometimes be rapid (over weeks); acromegalic features(^1,16)</td>
</tr>
<tr>
<td><strong>SUBCUTANEOUS FAT LOSS AREAS</strong></td>
<td>Face, neck, trunk, and extremities, as well as palms and soles(^16)</td>
</tr>
<tr>
<td><strong>SPARING FAT LOSS OR EXCESS FAT AREAS</strong></td>
<td>Degree of intra-abdominal fat varies(^1)</td>
</tr>
<tr>
<td><strong>METABOLIC ABNORMALITIES</strong></td>
<td>Diabetes mellitus, insulin resistance, hypertriglyceridemia(^1)</td>
</tr>
<tr>
<td><strong>CAUSE</strong></td>
<td>Presence of autoimmune diseases, especially juvenile dermatomyositis or panniculitis; can also be idiopathic(^1)</td>
</tr>
<tr>
<td><strong>FEMALE-SPECIFIC FEATURES</strong></td>
<td>Mild hirsutism and menstrual irregularity(^16)</td>
</tr>
</tbody>
</table>
| **OTHER FEATURES** | • Hepatosplenomegaly\(^16\)
• Acanthosis nigricans\(^16\)
• History of tender subcutaneous nodular swellings suggestive of panniculitis preceding the onset of lipodystrophy\(^16\)
• Presence of other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, or Sjögren syndrome\(^16\)
• Hyperphagia\(^1\)
• Proteinuric nephropathies\(^14\) |

Consequences

Metabolic abnormalities are common after AGL onset. Low HDL, hepatic steatosis, and acanthosis nigricans typically develop in childhood.\(^16,17\)

Approximately 50% of patients with AGL present with panniculitis or juvenile dermatomyositis prior to fat loss.\(^17\)

* Lateral view of an 8-year-old German boy with AGL. He started experiencing generalized loss of subcutaneous fat at age 3 with marked acanthosis nigricans in the neck, axillae, and groin. He developed Crohn’s disease at age 11, requiring hemicolectomy at age 13.\(^17\)
* Female patient with acquired generalized lipodystrophy. This patient has pancreatic beta cell failure and a low insulin concentration secondary to recurrent hypertriglyceridemia-induced pancreatitis.\(^20\)
KEY CLINICAL CHARACTERISTICS MAY LEAD TO EARLY DETECTION OF GENERALIZED LIPODYSTROPHY

The American Association of Clinical Endocrinologists (AACE) task force recommends considering a group of clinical characteristics that should raise the suspicion of generalized lipodystrophy.\(^1\)

Not all patients with the clinical characteristics listed below will have generalized lipodystrophy.

### CLINICAL CHARACTERISTICS THAT INCREASE THE SUSPICION OF GENERALIZED LIPODYSTROPHY\(^1,6\)

<table>
<thead>
<tr>
<th>Core clinical characteristic for generalized lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss or absence of subcutaneous body fat in a generalized fashion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supportive clinical characteristics for generalized lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presence of diabetes with evidence of severe insulin resistance</td>
</tr>
<tr>
<td>– Diabetes mellitus with requirement for high doses of insulin (eg, requiring (\geq 200) U/day, (\geq 2) U/kg/day, or currently taking U-500 insulin)</td>
</tr>
<tr>
<td>– Ketosis-resistant diabetes</td>
</tr>
<tr>
<td>• Other evidence of severe insulin resistance</td>
</tr>
<tr>
<td>– Acanthosis nigricans</td>
</tr>
<tr>
<td>– PCOS or PCOS-like symptoms (hyperandrogenism, oligomenorrhea, and/or polycystic ovaries)</td>
</tr>
<tr>
<td>• Presence of hypertriglyceridemia</td>
</tr>
<tr>
<td>– Severe hypertriglyceridemia ((\geq 500) mg/dL)</td>
</tr>
<tr>
<td>– Triglyceride levels that are nonresponsive to therapy and/or modifications to diet ((\geq 250) mg/dL)</td>
</tr>
<tr>
<td>– History of pancreatitis associated with hypertriglyceridemia</td>
</tr>
<tr>
<td>• Evidence of hepatic steatosis or steatohepatitis</td>
</tr>
<tr>
<td>– Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease (eg, viral hepatitis) may be consistent with nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td>– Radiographic evidence of hepatic steatosis (eg, on ultrasound or computed tomography)</td>
</tr>
<tr>
<td>• Family history of similar physical appearance and/or history of fat loss</td>
</tr>
<tr>
<td>• Prominent muscularity and phlebomegaly (enlarged veins) in the extremities</td>
</tr>
<tr>
<td>• Disproportionate hyperphagia (cannot stop eating, waking up to eat, fighting for food)</td>
</tr>
<tr>
<td>• Secondary hypogonadism in a male or primary/secondary amenorrhea in a female patient</td>
</tr>
</tbody>
</table>

Abbreviation: PCOS, polycystic ovary syndrome.

Genetic testing can rule in, but not rule out, CGL, as not all defective genes associated with CGL have been identified.\(^{17}\)
Generalized lipodystrophy includes 2 of the 4 major subtypes of lipodystrophy—CGL and AGL. Identifying the key clinical findings may help differentiate it from the other 2 subtypes.\(^1\)

Disease presentation may vary among individuals with generalized lipodystrophy. Not all individuals will present with the same findings.\(^1\)

### TO AVOID MISDIAGNOSIS, DISTINGUISH GENERALIZED LIPODYSTROPHY FROM OTHER SUBTYPES OF LIPODYSTROPHY\(^1\)

Generalized lipodystrophy includes 2 of the 4 major subtypes of lipodystrophy—CGL and AGL. Identifying the key clinical findings may help differentiate it from the other 2 subtypes.\(^1\)

Disease presentation may vary among individuals with generalized lipodystrophy. Not all individuals will present with the same findings.\(^1\)

### KEY

- ● = Essential finding
- ○ = Finding may be present

### CLINICAL FINDINGS OF THE MAJOR LIPODYSTROPHY SUBTYPES\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>CGL</th>
<th>AGL</th>
<th>FPL</th>
<th>APL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range of onset</strong></td>
<td>Infancy to early childhood</td>
<td>Childhood through adulthood</td>
<td>Childhood through adulthood</td>
<td>Childhood through adulthood</td>
</tr>
<tr>
<td>Approximate gender distribution (male:female)</td>
<td>1:1-2</td>
<td>1:3</td>
<td>1:1-2(^a)</td>
<td>1:4</td>
</tr>
<tr>
<td><strong>Fat loss locations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face and neck</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Chest/trunk</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td><strong>Fat accumulation/sparing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face and neck</td>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Hips and buttocks</td>
<td></td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lower extremities</td>
<td></td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td><strong>Other findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerated linear growth</td>
<td>○</td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Acromegalooid features</td>
<td>○</td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Umbilical prominence</td>
<td>○</td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Panniculitis</td>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Hyperandrogenism in females</td>
<td>○</td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

\(^{a}\) FPL is typically more readily recognized in females and affects females more severely.

Abbreviations: APL, acquired partial lipodystrophy; FPL, familial partial lipodystrophy. Adapted from Handelsman, *Endocr Pract*, 2013.
CASE STUDY
AFRICAN-AMERICAN FEMALE, AGE 19

Clinical presentation\textsuperscript{1,6,7,21,22}

- Prominent veins
- Hyperphagia
- Acromegaloid features
- Increased facial and body hair
- HbA1c: 8.5%
- Fasting glucose level: 174 mg/dL
- Fasting triglyceride level: 348 mg/dL
- Generalized absence of fat and muscular appearance (noted at birth)
  - Face, neck, chest and trunk, upper and lower extremities, and intra-abdominal region
- Acanthosis nigricans on back of the neck, axillae, and groin
- Hepatosplenomegaly with umbilical prominence
- Eruptive xanthomas

This case study is a hypothetical example based on collective information gathered from the experiences of patients with CGL.

<table>
<thead>
<tr>
<th>Age</th>
<th>Symptoms/Medical event</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Widespread loss of adipose tissue, Muscular hypertrophy</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>Progressive adipose tissue loss and muscular hypertrophy, Hyperphagia, Accelerated growth</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Acromegaloid appearance, Clitoromegaly</td>
<td>CGL</td>
</tr>
<tr>
<td>3</td>
<td>Hepatomegaly, Myocardial hypertrophy</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Hirsutism, Acanthosis nigricans</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Insulin resistance, Hypertriglyceridemia</td>
</tr>
<tr>
<td>12</td>
<td>Albuminuria detected</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Irregular periods</td>
<td>PCOS</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>Diabetes mellitus, Severe hypertriglyceridemia</td>
</tr>
<tr>
<td>19</td>
<td>Poor glycemic control despite metformin use (6000 mg/day)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical presentation\textsuperscript{16}

- Muscular appearance and prominent veins
- Increased facial and body hair
- HbA1c: 8.3%
- Fasting glucose level: 176 mg/dL
- Fasting triglyceride level: 350 mg/dL
- Hyperphagia
- 12.1% total body fat

- Generalized loss of fat
  - Face, arms, thighs, calves, and gluteal regions, as well as palms and soles
- Acanthosis nigricans on back of the neck, axillae, and groin
- Hepatosplenomegaly with protuberant abdomen
- Palpable liver and spleen

### Medical History\textsuperscript{1,16}

<table>
<thead>
<tr>
<th>Age</th>
<th>Symptoms/Medical event</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>• Skin rash</td>
<td>• Juvenile dermatomyositis</td>
</tr>
<tr>
<td></td>
<td>• Weak muscles</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>• Loss of fat from face, extremities, palms, and soles of feet</td>
<td>• Insulin resistance</td>
</tr>
<tr>
<td></td>
<td>• Hyperphagia</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>• AGL</td>
</tr>
<tr>
<td>13</td>
<td>• Irregular periods</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>• Severe hypertriglyceridemia</td>
</tr>
<tr>
<td>15-25</td>
<td>• Poor glycemic control despite high daily insulin dose (U-500)</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>• High blood pressure</td>
<td>• Hypertension</td>
</tr>
</tbody>
</table>

This case study is a hypothetical example based on collective information gathered from the experiences of patients with AGL.
IDENTIFYING KEY CLINICAL CHARACTERISTICS MAY LEAD TO EARLY DETECTION OF GENERALIZED LIPODYSTROPHY

- Generalized lipodystrophy (GL) is a rare, complex, and clinically heterogeneous disorder characterized by the widespread lack or loss of subcutaneous adipose tissue in most or all parts of the body, and the associated loss of endocrine function, resulting in relative leptin deficiency.

- Relative leptin deficiency results in metabolic abnormalities such as:
  - Diabetes mellitus requiring high doses of insulin (U-500)
  - Hypertriglyceridemia: ≥500 mg/dL
  - Insulin resistance
  - Hyperphagia

- Metabolic abnormalities may lead to serious comorbidities in GL patients.

- There are 2 types of GL:
  - CGL presents with a generalized lack of adipose tissue and prominent muscularity
  - AGL presents with adipose tissue loss in a generalized fashion over time

- Per the AACE guidelines, key clinical characteristics may lead to early detection of GL.

- To avoid misdiagnosis, distinguish GL from other subtypes of lipodystrophy.

References: