# Visus Light Perception and Severe Hypertriglyceridemia in Partial Lipodystrophy Syndrome with Normal Adiponectin Level

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## Abstract

Partial lipodystrophy syndrome is a disorder of adipose tissue formation. This disorder is characterized by the loss of subcutaneous tissue in the extremities with buildup of fat around the face, neck or stomach. Partial lipodystrophy also causes severe insulin resistance which develops into diabetes, severe hypertriglyceridemia, and cardiovascular disease. We report a case of a patient with clinical and laboratory suspicion of partial lipodystrophy syndrome. The case observed in this study was a 27-year-old woman who suffered from severe abdominal pain along with nausea and vomiting. She was diagnosed with diabetes mellitus (DM) at the age of 10 and has used insulin since the age of 19. According to physical examination, her stats were: blood pressure 180/110 mmHg, pulse 107×/minute, anemic conjunctiva, visus light perception, hepatosplenomegaly, acanthosis nigricans (+), thigh circumference 23 cm, BMI: 21.6. Laboratory results: Hb 8g/dL, platelets $76\times10^3$/µL, pre-prandial glucose 143 mg/dL, pre-prandial insulin 13.5 µIU/L (normal), C-peptide 4.8 ng/mL (increase), adiponectin 5.47 µg/ml (normal), HOMA-IR 4.8 (increase), HOMA-B 60.9 (decrease), HbA1C 11.1%, triglycerides 2.648 mg/dL, total cholesterol 581 mg/dL, LDL 128 mg/dL, TG/HDL ratio 51.9 (increase), BUN 32 mg/dL, serum creatinine 2.14 mg/dL, negative urine ketones, and proteinuria 4+. Visus light perception is caused by diabetic retinopathy. Partial fat accumulation in the face and stomach along with decrement of subcutaneous fat in extremities raise suspicion of partial lipodystrophy. This statement is supported by signs of severe insulin resistance such as severe hypertriglyceridemia (>1000 mg/dL), increase of TG/HDL ratio and onset DM at the age of 10. Normal adiponectin can be found in partial lipodystrophy. Therefore, it can be concluded that visus light perception, severe hypertriglyceridemia and insulin resistance signed by the increase of HOMA-IR and TG/HDL ratio with DM at a young age shows a complication of partial lipodystrophy syndrome.

***Keywords:*** *Partial Lipodystrophy, Insulin Resistance, Adiponectin.*

## Introduction

Lipodystrophy syndrome is a very rare disorder characterized by a deficiency in fatty tissue causing metabolic complications such as diabetes, hypertriglyceridemia and steatohepatitis. Lack of fat tissue is not caused due to nutritional deficiencies or catabolic conditions. Lipodystrophy syndrome is classified based on etiology, namely lipodystrophy caused by genetic disorders or acquired. This syndrome is also divided based on the distribution of fat tissue loss, namely generalized lipodystrophy syndrome which affects the whole body and partial lipodystrophy syndrome which affects a certain region of the body. This results in 4 categories of lipodystrophy syndrome, namely congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial

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lipodystrophy (APL)[1].

Lack of adipose tissue causes ectopic accumulation of lipid in various organs such as muscles, liver and other organs. This deficiency of adipose tissue also causes insulin resistance which can lead to diabetes, hypertriglyceridemia and fatty liver. Partial lipodystrophy syndrome is characterized by the lack of adipose tissue in the limbs, such as in the arms and legs, as well as the buttocks and hips. The accumulation of fat in certain parts of the body may result in physical appearance resembling Cushing's syndrome. Fat distribution is usually normal during childhood, then a subsequent loss of fat tissue occurs during puberty. Metabolic complications often happen in young adults[2].

The diagnosis of lipodystrophy syndrome is based on history, physical examination, body composition and metabolic status. Until this day, there is no known leptin level examination that can be used to establish or exclude a diagnosis of lipodystrophy syndrome. Genetic confirmatory testing is required when familial lipodystrophy is suspected, while complement and autoantibody examinations are required in the diagnosis of acquired lipodystrophy syndrome. The definitive diagnostic criteria for lipodystrophy syndrome is still unknown[3].

**Case**

Ms. M, 27 years old, came to the emergency room alone with complaints of intermittent abdominal pain in the gut since the last 2 weeks. The patient also complained of nausea and vomiting since the last 1 month, intermittent. Patient's vomit had the same color as the food the patient consumed, with frequency of 4-5 times per day. The patient had liquid stool since the last 2 weeks, with a frequency of 3-4 times per day, no blood or mucus was present. There was no fever and the patient's urine were normal.

**Past Medical Record**

- The patient began to frequently get sick at 8 years old. According to the patient's history, the patient went to the children's endocrine clinic at Dr. Soetomo Hospital because patient's body was always thin. At that time, the patient was diagnosed with diabetes mellitus and patient started using insulin at the age of 19.

- Since the last 2 years, patient visited an internal medicine endocrine clinic, then in the last 1 year, insulin injections were replaced with acarbose and glimepiride. However, in the recent months, patient did not visit the doctor and did not take any medication.

- Latest record, patient visited RSDS eye clinic complaining about blurred vision, and was diagnosed with diabetic retinopathy and glaucoma.

**Family Medical Record**

Patient is the 3rd child of 3 siblings, with both siblings diagnosed with diabetes mellitus. The patient's mother admitted that she does not suffer from diabetes, while the patient's father has no known medical records and passed away from a hemorrhagic stroke.

**Physical Examination**

GCS: E4V5M6, General condition: weak

BP: 180/110, HR: 107, RR: 20, Temp: 36.7, $SpO_2$: 99%

- Head neck: exophthalmus in both eyes, anemic in both conjunctivae.

- Thorax: symmetrical, no retraction.

§ Pulmo: vesicular, no ronchi and wheezing.

§ Cor: first and second heart sounds produce single sound, no murmurs and gallops.

- Abdomen: distention, increased bowel sounds, tenderness in all areas of the abdomen with maximum tenderness in the epigastric and umbilical regions. Hepatomegaly as big as 3 fingers under the arcus ribs along with splenomegaly as big as Schuffner 2 Hocket 2 was present. No mass was felt.

- Extremities: hypopigmented macula in the crurisdextra et sinistra region was present, no edema, dry and warm.

**Laboratory**

**Table 1. Hematology Results of Patients**

| Hematology | 17/07/19 (Emergency Department) | 19/07/19 | 22/07/19 | Reference Interval |
|---|---|---|---|---|
| WBC x (103/µL) | 4.38 | 4.19 | 4.4 | 3.6-10.6 |
| % Neu | 78.1 | 77.3 | 63 | 50-70 |
| % Lym | 17.8 | 19.6 | 28.4 | 18-42 |
| % Mono | 2.3 | 3.1 | 6.6 | 02-Nov |
| % Eos | 1.6 | 0 | 2 | 01-Mar |
| % Baso | 0.2 | 0 | 0 | 0-2 |
| RBC x 106/µL | 2.94 | 3.05 | 2.99 | 3.8-5.2 |
| Hb g/dL | 8 | 8.3 | 7.9 | 11.7-15.5 |
| Hct % | 22.2 | 23.3 | 22.3 | 34-36 |
| MCV fL | 75.5 | 76.4 | 74.6 | 81-99 |
| MCH pg | 27.2 | 27.2 | 26.4 | 28-33 |
| MCHC g/dL | 36 | 35.6 | 35.4 | 32-36 |
| RDW % | 14.1 | 14.2 | 13.9 | 11.5-14.5 |
| Plt x 103/µL | 76 | 82 | 86 | 150-450 |
| PPT (s) | 11.4 | 9.8 | - | 9-12 |
| APTT(s) | 32 | 29.1 | - | 23-33 |

**Table 2. Clinical Chemistry Results of Patient**

| Clinical Chemistry | 17/07/19 (Emergency Department) | 18/07/19 | 19/07/19 | 22/07/19 | Reference Interval |
|---|---|---|---|---|---|
| BUN (mg/dL) | 31 | - | 22 | 34 | 10-20 |
| SK (mg/dL) | 2.11 | - | 2.87 | 2.62 | 0.5-1.2 |
| Glucose Level (mg/dL) | 175 | - | 177 (Pre-prandial) | - | <110 |
| Direct Bilirubin (mg/dL) | 0.04 | - | - | - | <0.2 |
| Total Bilirubin (mg/dL) | 0.23 | - | - | - | 0.2-1 |
| AST (U/L) | 26 | - | 15 | 11 | 0-35 |
| ALT (U/L) | 33 | - | 25 | 8 | 0-35 |
| Albumin (g/dL) | 3.6 | - | 3.2 | 2.9 | 3.4-5 |
| Na (mmol/L) | 138 | - | | 135 | 136-145 |
| K (mmol/L) | 4.9 | - | | 3.8 | 3.5-5.1 |
| Cl (mmol/L) | 101 | - | | 99 | 98-107 |
| Amylase (U/L) | - | 24 | - | 30 | 25-115 |
| Lipase (U/L) | - | 124 | - | 88 | 73-393 |
| HbA1C | | 11.1% | | | 4.5-6 |
| Pre-prandial Insulin (µIU/L) | | | 13,5 | | 2-25 |

***Cont...*** **Table 2. Clinical Chemistry Results of Patient**

| | | | | | |
|---|---|---|---|---|---|
| C-peptide (ng/Ml) | | | 4.8 | | 0.78-1.89 |
| Adiponectin (µg/ml) | | | 5.47 | | 3.58-9.66 |
| HOMA-B (%) | | | 60.9 | | 70-150 |
| HOMA-IR | | | 4.8 | | <2.5 |

**Table 3. Lipid Profile of Patient**

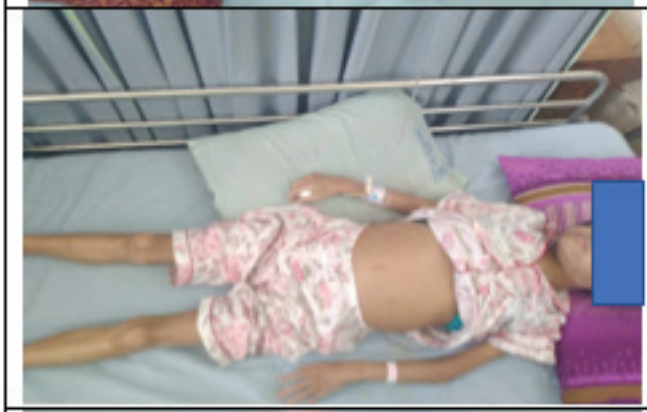
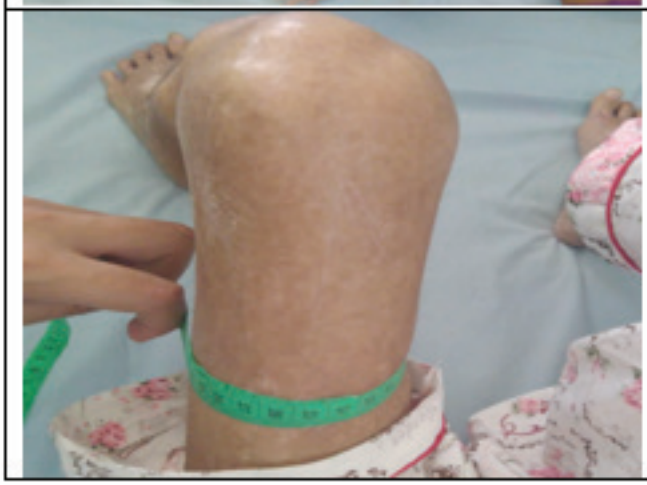
| Lipid Profile | 17/7/19 | 19/7/19 | 22/7/19 | Reference Interval |
|---|---|---|---|---|
| Cholesterol Total (mg/dL) | 581 | 412 | 545 | <200 |
| Cholesterol-LDL (mg/dL) | 128 | 121 | 214 | <100 |
| Cholesterol-HDL (mg/dL) | 51 | 55 | 57 | 40-60 |
| Triglyceride (mg/dL) | 2648 | 1850 | 1033 | 30-150 |
| Ratio TG/HDL | 51.9 | | | < 3 |

**Table 4. Urinalysis Results of Patient**

| Urinalysis | 17/07/2019 |
|---|---|
| Glucose | +/- |
| Bilirubin | Negative |
| Ketones | Negative |
| Density | 1.015 |
| Blood | Negative |
| pH | 5.5 |
| Protein | 4+ |
| Urobilinogen | 0.2 E.U/dL |
| Nitrite | Negative |
| Leukocyte | Negative |
| Color | Orange |
| Clarity | Clear |

**Anthropometry: Weight: 58 kg; Height: 164 cm; BMI: 21.6 kg/m$^2$ (Normal: 18.5-25 kg/m$^2$).**

**Table 5. Patient's conditions**

| | |
|---|---|
|  | Accumulation of fat can be seen on the face. There is a decrease of fat tissue in the arms. |
|  | Accumulation of fat in the abdomen can be seen. |
|  | Thigh circumference 23 cm (N: 45-55) |

**Therapy Instructions**

- Inj. Novorapid 4 units every 8 hours before meal SC
- Inj. Levemir 8 units every 24 hours, night time SC
- Thiazolidinedione 100 mg 2×1
- Tab. Amlodipine 10 mg every 24 hours PO (night time)
- Tab. Lisinopril 5 mg every 24 hours PO (morning)

## Discussion

Onset of diabetes mellitus with age <25 years, insulin resistance overview based on increase of C-peptide, HOMA-IR, TG/HDL ratio and slight decrease in HOMA-B, and normal adiponectin levels show signs of partial lipodystrophy syndrome. Lipodystrophy syndrome is suspected in a patient when the patient has total or regional deficiency of fatty tissue based on physical examination supported by anthropometric data. Adiponectin assay is still unstandardized and can give normal results, especially in partial type cases. Lipodystrophy syndrome can be difficult to distinguish from uncontrolled diabetes mellitus because both can cause hypertriglyceridemia, although glucose control in diabetes can restore fat tissue, whereas in lipodystrophy it cannot. Analysis of family medical records can help differentiate diagnosis of acquired or genetic lipodystrophy syndrome, although new mutations may occur. The presence of autoimmune disease and/or decrease in C3 and C4 can support the diagnosis of acquired lipodystrophy syndrome. Lipodystrophy is suspected if any of the following symptoms are found[4]:

- Essential Point

§ Generalized or partial fat tissue deficiency.

- Physical Examination

§ Growth failure (infants or children)

§ Prominent muscles

§ Severe nigricans acanthosis

§ Cushingoid appearance

- Metabolic Overview

§ Diabetes requiring high doses of insulin, more than 2U/kg/day

§ Severe hypertriglyceridemia (>500 mg/dL) with or without therapy; or >250 mg/dL with diet and medicine

§ History of pancreatitis due to hypertriglyceridemia

§ Non-alcoholic steatohepatitis in non-obese people

§ Significant hyperphagia

Hyperphagia is caused by the lack of leptin which correlates with remaining fat tissue. Severe insulin resistance is compensated by hyperinsulinemia or often manifests as diabetes in the second decade. Insulin resistance is characterized by the increase of HOMA-IR and TG/LDL ratio in the patient. Decreased HOMA-B can be caused by high glucose levels for a long period of time causing glucose toxicity which triggers excessive free radical production and results in damage to β-pancreatic cells. Hepatomegaly and splenomegaly are commonly found. Adiponectin serum, sex hormone binding globulin, and insulin like growth factor binding protein 1 often have low levels and are useful for lipodystrophy syndromes from insulin receptor defects which also suggest a deficiency of fatty tissue[5,9].

FPLD is inherited in an autosomal dominant manner and often manifests clinically when entering puberty. Lack of fatty tissue is often found in the limbs and buttocks, but sometimes excess fat can be found on the face and neck. FPLD is clearly evident on women because women have more femorogluteal fat than men. The clinical symptoms of FPLD in women are also more severe than in men. Clinical manifestations vary from mild impaired fasting glucose to severe insulin resistance and severe dyslipidemia. Cardiovascular diseases are also commonly found[6].

FPLD is frequently associated with mutations in the function loss of the PPAR-G gene that regulates PPARγ synthesis. PPARγ is an insulin hormone receptor in the nucleus which is widely expressed in fat tissues. These receptors play a role in the differentiation of fatty tissue and are often associated with lipodystrophy. However, PPARγ defects are more often associated with partial lipodystrophy. PPARγ mutations are related to the inability in regulating postprandial lipid due to the absence of adipose tissue. Adipose tissue acts as a buffer for fat intake[2].

In addition, lipodystrophy is also often associated with mutations in AKT, which is an intracellular receptor for insulin. Insulin is a stimulator of adipogenesis and mediates glucose uptake into adipose tissue.

Hence, this mutation causes severe insulin resistance. Compensation for insulin resistance is the occurrence of hyperinsulinemia which then causes lipogenesis stimulation in the liver[2].

One of the conservative therapies for lipodystrophy syndrome is using thiazolidinediones. This drug has the ability to increase the sensitivity of cells towards insulin. This increased sensitivity can lead to adipogenesis. Patients with partial lipodystrophy syndrome experience fat accumulation in the visceral fat tissue around the abdomen. This is to compensate the inability to form fat tissue in the extremities. The accumulation of visceral fat is very dangerous and can cause cardiovascular disorders. Visceral fat tissue secretes many proinflammatory cytokines such as IL-6 and TNF-α[2].

The prognosis for partial lipodystrophy is still uncertain due to the rarity of the case. Most of the severity is determined by metabolic complications such as the severity of diabetes, pancreatitis and cardiovascular diseases. The course of the disease tends to be progressive. Premature deaths often result from atherosclerosis such as myocardial infarction at a young age. Many deaths are also caused by infection due to weakened immune system because of diabetes. The use of insulin sensitivity enhancing drugs such as thiazolidinone and leptin analogues help reduce patient symptoms, prevent complications and increase life expectancy. Most patients can reach life expectancy of 60 years old while the average mortality rate is 30-40 years old[5,9].

## Conclusion

Lipodystrophy syndrome is a very rare disorder characterized by a deficiency in fatty tissue causing metabolic complications such as diabetes and hypertriglyceridemia. Adiponectin assay is still unstandardized and can give normal results, especially in partial type cases. Partial lipodystrophy syndrome is characterized by the lack of adipose tissue in the limbs, such as in the arms and legs, as well as the buttocks and hips. Accumulation of fat in certain parts of the body can be found, which may give physical resemblance of Cushing's syndrome. Fat distribution is usually normal during childhood, while during puberty, subsequent loss of fat tissue occurs. Metabolic complications are common in young adults.

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## References

1. Brown RJ, Araujo-vilar D, Cheung PT, *et al*. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. 2016; 101(12):4500–11.
2. Huang-doran I, Sleigh A, Rochford JJ, *et al*. Lipodystrophy: metabolic insights from a rare disorder. 2010; 207(3): 254-255.
3. Raisa A, Santos J, Ferreira SP, *et al*. Dunnigan-Type Familial Partial Lipodystrophy: Understanding and Treating the Syndrome. 2017; 7(1): 22–34.
4. Tonkin AM. Therapeutic Strategies in Lipid Disorders. Oxford UK: Atlas Medical Publishing Ltd; 2009.
5. Fiorenza CG, Chou SH, Mantzoros CS. Lipodystrophy: Pathophysiology and Advances in Treatment. 2011; 7(3):137–150.
6. Handelsman Y, Oral EA, Zachary T, *et al*. The clinical approach to the detection of lipodystrophy – an AACE consensus statement. 2013; 19(1):107–116.
7. DeFronzo RA, Ferrannini E, Zimmet P, *et al*. International textbook of diabetes mellitus 4th edition. Philadelphia: Elsevier; 1233-1234; 2015.