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Approach to the Patient

Approach to Diagnosing a Pediatric Patient With Severe Insulin Resistance in Low- or Middle-income Countries

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Abstract

Diabetes mellitus (DM) in children is most often caused by impaired insulin secretion (type 1 DM). In some children, the underlying mechanism for DM is increased insulin resistance, which can have different underlying causes. While the majority of these children require insulin dosages less than 2.0 U/kg/day to achieve normoglycemia, higher insulin requirements indicate severe insulin resistance. Considering the therapeutic challenges in patients with severe insulin resistance, early diagnosis of the underlying cause is essential in order to consider targeted therapies and to prevent diabetic complications. Although rare, several disorders can contribute to severe insulin resistance in pediatric patients. Most of these disorders are diagnosed through advanced diagnostic tests, which are not commonly available in low- or middle-income countries. Based on a case of DM
with severe insulin resistance in a Surinamese adolescent who was later confirmed to have autosomal recessive congenital generalized lipodystrophy, type 1 (Berardinelli–Seip syndrome), we provide a systematic approach to the differential diagnosis and work-up. We show that a thorough review of medical history and physical examination generally provide sufficient information to diagnose a child with insulin-resistant DM correctly, and, therefore, our approach is especially applicable to low- or middle-income countries.

Key Words: Diabetes mellitus, insulin resistance, low- or middle-income country, children, lipodystrophy, Berardinelli–Seip syndrome

Case Presentation—Part 1

A 15-year-old girl from Maroon (African descent) presented at a rural outpatient clinic in the Surinamese inland with headaches, dizziness, blurred vision, polyuria, polydipsia, and weight loss for 10 months. She had menarche at the age of 11 years, and had regular menstrual cycles till age 14 years, when she developed amenorrhea.

She had no positive family history of genetic, endocrine, or autoimmune disorders. It is unknown whether there is consanguinity among the parents. She lived in a small village in the jungle with her mother. Her alleged father lives in French Guiana. She did not take any medication or traditional drugs.

On physical examination she had a striking muscular appearance with near generalized lack of body fat and coarse facial features with a prominent jaw (Fig. 1A-1C). She had large hands and feet. She had mild acanthosis nigricans in the posterior cervical region and axillae (Fig. 1D). She had normal subcutaneous fat on her palms and soles (Fig. 1E and 1F). There was no buffalo hump, hirsutism, or stretch marks. Abdominal examination showed umbilical protuberance and the liver was palpable 1 cm below the costal margin. Tanner staging was postpubertal with normal breast development, and axillary and pubic hair. Anthropometric measures (World Health Organization 2007 growth references) showed a height of 140 cm (Z-score height for age < –3), a weight of 35 kg, a body mass index of 17.8 kg/m² (Z-score for age –1 SD), and a head circumference of 52 cm. Her vital signs were normal.

Her capillary blood glucose was unmeasurably high. She immediately received a dose of 8 IU of insulin (Mixtard®) subcutaneously and was transferred to the Academic Hospital of Paramaribo, Suriname.

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Figure 1. Photographs of the 15-year-old female patient. (A) Anterior view and (B) posterior view: note the muscular appearance with near total lack of body fat and umbilical protuberance. Breast development was normal. (C) Axillae and face: note the acanthosis nigricans in the axillae and the prominent jaw. (D) Posterior view of the neck demonstrating mild acanthosis nigricans. (E and F) Normal subcutaneous fat distribution on the palms and soles.
Routine biochemical blood tests on admission (Table 1) showed marked hyperglycemia with blood glucose of 33.7 mmol/L (normal range 4.6-5.5 mmol/L) without ketosis or acidosis on capillary blood gas. Kidney and liver function tests were normal. Blood hemoglobin A1c (HbA1c) was 20.9% (204.9 mmol/mol, normal range 20-42 mmol/mol). Serum gonadotropin and estradiol levels were within reference ranges (Table 2). The low endogenous insulin level can be attributed to the subcutaneous insulin administration 12 hours before the measurement. A urinary pregnancy test was negative.

### Table 1. Biochemical blood tests performed on admission

| Analyte           | Value       | Reference range |
|-------------------|-------------|-----------------|
| Glucose, mmol/L   | 33.7a       | 4.0-6.5         |
| HbA1c %; mmol/mol | 20.9; 204.9a| 4.0-6.0; 20-42  |
| Urea, mmol/L      | 2.6c        | 3.0-7.0         |
| Creatinine, µmol/L| 44c         | 60-110          |
| Sodium, mmol/L    | 128b        | 132-148         |
| Potassium, mmol/L | 3.5b        | 3.6-5.0         |
| Phosphate, mmol/L | 1.08        | 1.00-1.60       |
| AST, IU/L         | 30          | 0-38            |
| ALT, IU/L         | 31          | 0-41            |
| LD, IU/L          | 91b         | 98-192          |
| CK, IU/L          | 48          | 38-174          |
| CRP, mg/dL        | 1.4a        | 0.0-0.5         |
| Hemoglobin, mmol/L| 7.5         | 7.5-9.9         |
| Leucocytes, ×10⁹/L| 3.8a        | 4.5-11.0        |
| Thrombocytes, ×10⁹/L| 298        | 150-400         |
| pH (venous)       | 7.40        | 7.35-7.45       |
| pCO₂ (venous), mmHg| 41.3       | 41-51           |
| HCO₃⁻ (venous), mmol/L | 24.8     | 23-29           |
| Base excess (venous), mmol/L | 0.8 | -2-2            |
| Ketones           | 0.0         | <0.6            |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatinine kinase; CRP, C-reactive protein; HbA1c, hemoglobin A1c; LD, lactate dehydrogenase.

aValue outside the reference range.

### Table 2. Endocrine tests performed on day 3 of admission

| Hormone level        | Value       | Reference range |
|----------------------|-------------|-----------------|
| Insulin, µIU/mL³     | <2.00b      | 9.3-29.1        |
| FSH, mIU/mL          | 1.6         | 0.7-11.1        |
| LH, mIU/mL           | 0.4         | 0.4-7.6         |
| Estradiol, pmol/L    | 300         | 100-1200        |
| Prolactin, ng/mL     | 4.1         | 1.9-25.0        |
| TSH, µIU/mL          | 0.95b       | 1.9-25.0        |
| Free thyroxine, ng/dL| 0.8         | 0.8-1.8         |
| Cortisol, nmol/L (9 AM)| 422        | 138-690         |

Abbreviations: FSH, follicle stimulating hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone.

bValue outside the reference range.

She was admitted and treated with subcutaneous intermediate acting insulin (Mixtard⁵) twice daily. Despite increasing dosages of intermediate acting insulin (up to 60 units per day) and concomitant short acting insulin (Actrapid⁶; up to 20 units per day), her fasting, preprandial, postprandial, and random blood glucose levels were consistently above 12 mmol/L and often between 20 and 30 mmol/L. After 2 months, her daily insulin requirements exceeded 2 IU/kg/day, indicating severe insulin resistance. Given her physical appearance, the high insulin requirements and uncontrolled blood glucose levels, we assumed that a diagnosis of type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) did not fit our case. A written informed consent was taken for genetic testing as well as for publication of her case and photographs.

### Background of Diabetes Mellitus and Insulin Resistance in Children

Diabetes mellitus (DM) is characterized by signs and symptoms of chronic hyperglycemia due to defects in insulin secretion, insulin action, or both (1). T1DM is responsible for the majority of pediatric cases, followed by T2DM. Rare forms of DM are monogenic diabetes (1-4% of pediatric diabetes cases), secondary to pancreatic diseases, endocrinopathy-related diabetes, drug- or chemical-induced diabetes, and various genetic syndromes (1, 2).

Each year, an estimated number of 98 000 new cases with DM under the age of 15 years are diagnosed worldwide. The incidence is increasing in many countries, with an overall annual increase estimated at around 3% (3). Although varying widely in incidence and prevalence, T2DM is becoming more common in the adolescent population. While T2DM represented approximately 3% of pediatric diabetes in 1991 in the United States (4), it currently accounts for 8% to 45%, depending on the studied population (5). The highest prevalence of T2DM among 15-19 year olds has been reported to be 51 per 1000 for Pima Indians in Arizona, United States, 4.5 for all US American Indians, and 2.3 for Canadian Indians (1).

Due to its rising incidence, DM is a public health challenge of increasing importance (6). Although morbidity and mortality rates in developed countries decreased as a result of education, more accurate treatment programs, and new technological interventions (7), it continues to be a severely disabling and lethal disease in developing countries due to limited access to treatment and self-care tools (3). Optimal care as described in guidelines can generally not be provided in low- and middle-income countries, which results in higher rates of disease-related complications and mortality (8).
Insulin therapy is life saving and lifelong in most pediatric cases, especially in T1DM (3). Some individuals, including T2DM patients, require high doses of insulin to maintain adequate blood glucose levels due to insulin resistance. T1DM patients require around 0.3 to 0.8 U/kg/day of insulin on average, with an increase during puberty to 1.0 to 1.5 U/kg/day, while T2DM patients require 1.0 to 2.0 U/kg/day. Rarely, insulin dosing within this range is not sufficient to maintain adequate glucose levels. Insulin requirements above 2.0 U/kg/day are classified as severe insulin resistance; requirements above 3.0 U/kg/day meet the criteria of extreme insulin resistance (9).

As a response to insulin resistance, the pancreatic beta cells increase insulin secretion, resulting in abnormally high blood insulin levels. Clinically, the first signs of hyperinsulinemia include acanthosis nigricans (a dermatosis characterized by thickened, hyperpigmented plaques, typically of the intertriginous surfaces and neck) likely due to insulin cross reacting with the insulin-like growth factor (IGF)-1 receptor (10). Other clinical manifestations of hyperinsulinism in women include polycystic ovaries, menstrual irregularities, and hyperandrogenism (11).

Since proper glycemic control is of utmost importance to avoid future diabetic complications, early diagnosis and targeted treatment are essential in cases of severe insulin resistance in children. Recently, a comprehensive review of severe insulin resistance syndromes (IRSs) categorized by disease process was published (12). A comprehensive approach to the diagnostic process in children, primarily based on clinical data and thus applicable in countries with limited resources is lacking. Hence, based on our unique case, we present a clinical approach to the pediatric patient with severe insulin resistance.

Differential Diagnosis in Pediatric Patients with Diabetes and High Insulin Requirements

Different underlying disorders can cause severe insulin resistance in children and adolescents. However, most are very rare and can only be diagnosed using specialized diagnostic laboratory methods or genetic screening that are not generally available in low- and middle-income countries.

Type A Insulin Resistance Syndrome

This rare hereditary (mostly autosomal dominant) syndrome has a prevalence of approximately 1 in 100,000 people and is caused by pathogenic variants in the insulin receptor (INSR) gene (13). Altered INSR-mediated signal transduction causes decreased sensitivity to insulin and impaired glucose regulation (14). Mostly women are affected, and it typically presents during adolescence, in nonobese individuals. Clinical manifestations include acanthosis nigricans, hyperandrogenism, and oligomenorrhea. The syndrome can only be confirmed by genetic testing. Laboratory tests that increase the likelihood of type A IRS include low to normal serum triglyceride levels, and elevated adiponectin levels (9).

The Rabson–Mendenhall and Donohue syndromes are 2 severe autosomal recessive insulin resistance disorders due to biallelic variants in INSR. Rabson–Mendenhall syndrome presents in childhood and is characterized by growth retardation, acanthosis nigricans, hirsutism, dental and ungual dysplasia, enlargement of the genitalia, and precocious puberty. Due to the lack of adequate therapy, the life expectancy after diagnosis is 1-2 years. Donohue syndrome, also known as leprechaunism, is lethal in early childhood (1-2 years of age) and is beyond the scope of this article (9, 15).

Type B Insulin Resistance Syndrome

This rare syndrome, reported so far in about 115 patients, is caused by acquired polyclonal autoantibodies against the INSR, which either block or stimulate the insulin receptor (16, 17). It mostly affects middle-aged black women and is often associated with other autoimmune diseases. It is less common in children. Clinically, patients develop extreme insulin resistance and hyperglycemia alternating with hypoglycemia. In contrast to type A IRS, transient hyperglycemic periods and spontaneous recovery can occur (17, 18). Typically, these patients have a characteristic distribution of acanthosis nigricans, involving perioral, perioral, and labial regions, and can also develop ovarian hyperandrogenism (9). Laboratory tests show low to normal serum triglyceride concentrations, and elevated adiponectin levels (19).

Type C Insulin Resistance Syndrome

This syndrome is known as the HAIRAN syndrome: hyperandrogenism, insulin resistance, acanthosis nigricans. This rare syndrome can be observed in women and is regarded as a subphenotype of polycystic ovary syndrome (PCOS). Clinical symptoms most often develop in adolescence (20). Data on incidence are lacking and there is no gold standard of diagnostic testing. Table 3 provides an overview of the various insulin resistance syndromes.

Endocrinopathies

Multiple endocrinopathies, such as acromegaly and Cushing’s syndrome, have been associated with insulin resistance, often with different underlying mechanisms (21).
Acromegaly is a rare clinical syndrome caused by excessive growth hormone (GH) production and increased circulating IGF-1 concentrations. A frequent complication of acromegaly is hyperglycemia. The prevalence of diabetes in patients with acromegaly ranges from 12% to 37.6% (22). The most important mechanism is insulin resistance due to excess GH and IGF-1 concentrations (23). Acromegaly patients typically have a lean phenotype with little visceral fat, coarse facial features, and signs of gigantism, including tall stature and large hands and feet. Acromegaly is extremely rare in children and incidence remains unknown (24).

Excess of the glucocorticoid hormones, due to overproduction of cortisol (endogenous) or due to prolonged use of high doses of glucocorticoids (exogenous), is the hallmark feature of Cushing’s syndrome (25). Although Cushing’s syndrome may occur in childhood, the adrenocorticotropic hormone (ACTH)–secreting adenoma—also named Cushing’s disease—accounts for 75% to 80% of endogenous Cushing’s syndrome in children and most commonly presents in adolescence (26). Patients have excess body fat with buffalo hump, supraclavicular fat pads, and may have purple striae.

Neuroendocrine Tumors
Gastroenteropancreatic neuroendocrine tumors are a heterogeneous group of rare neoplasms, secreting peptides and neuroamines causing paraneoplastic syndromes (27). Among these tumors is pheochromocytoma, a tumor originating from the adrenal medulla, secreting catecholamines. These catecholamines can induce or aggravate insulin resistance and reduce insulin secretion (28). However, patients with pheochromocytoma often present with other symptoms, such as hypertension, tachycardia, diaphoresis, and headaches.

Anti-insulin Antibodies
Rarely, an individual can develop antibodies against either endogenous or exogenous insulin, leading to insulin resistance. When antibodies to endogenous insulin are present, the condition is known as insulin autoimmune syndrome. Antibodies against exogenous insulin are rarely clinically significant, although coexistent insulin allergy cases have been described (9).

Subcutaneous Insulin Resistance
Cases have been reported of subcutaneous insulin resistance with normal sensitivity to intravenously administered insulin. The supposed mechanism is degradation of exogenous insulin by adipose and muscle tissue (29).

Medications
Some medications affect glucose metabolism and can induce insulin resistance, however it is rarely severe. Examples of such drugs are thiazide diuretics, nicotinic acid, high doses of fluoroquinolones, pentamidine, phenytoin, valproic acid, second-generation antipsychotics, antidepressant agents, theophylline, glucocorticoids, interferon alpha, calcineurin inhibitors, oral contraceptives, GH therapy, somatostatin analogues, and HIV-1 protease inhibitors (9, 30).

Lipodystrophy Syndromes
These rare syndromes are characterized by the selective absence of body fat (31). The subtypes are classified as genetic and acquired, based on the etiology, and as generalized or partial, depending on the distribution of the fat loss. Among the genetic lipodystrophies, congenital generalized lipodystrophy (CGL) presents with near total loss of body fat at birth or shortly thereafter (32). Insulin-resistant DM usually develops during teenage years in CGL patients but has been reported as early as at birth and during infancy. The other common subtype of genetic lipodystrophies is familial partial lipodystrophy (FPLD). FPLD patients have normal body fat at birth and during early childhood, but they start losing subcutaneous fat from the limbs and gluteal region during late childhood or around puberty (33). In some FPLD patients, body fat accumulation can occur on the face, neck, and inside the abdomen, resulting in Cushingoid features. Besides CGL and FPLD, there are other extremely rare forms of genetic lipodystrophies.

Both nongenetic forms of lipodystrophy, namely acquired generalized lipodystrophy (AGL) and acquired partial lipodystrophy (APL), are often associated with autoimmune disorders, have a female predominance, and usually start around adolescence (34, 35). Patients with AGL lose nearly all subcutaneous fat during childhood and can have associated autoimmune diseases, panniculitis, or may be idiopathic (34). These patients can also present with extremely insulin resistant DM during childhood. In APL, the typical pattern of fat loss consecutively affects the face, neck, shoulders, arms, and trunk, whereas fat accumulation appears in the hips, buttocks and legs (35). APL patients, however, do not develop DM during childhood. Almost all forms of lipodystrophy can be accompanied by hirsutism, acanthosis nigricans, hypertriglyceridemia,
nonalcoholic fatty liver disease (NAFLD), and severe insulin resistance. However, in APL, metabolic complications are rare (35-37).

Other Genetic Syndromes

Severe insulin resistance has been reported in several other genetic syndromes associated with severe obesity, such as Alström or Bardet–Biedl syndrome. A notable group of disorders which are associated with severe insulin resistance are those associated with DNA repair defects or progeria, including Werner Syndrome, Bloom Syndrome and mandibuloacral dysplasia. The insulin resistance in these rare genetic syndromes is often part of a larger spectrum of abnormalities and therefore out of the scope of this article (11, 15).

Clinical Work-up of Severe Insulin Resistance

In patients with hyperglycemia with severe insulin resistance, a systematic approach to investigate differential diagnoses is essential. A thorough assessment of medical history and physical examination can guide a clinician to the correct diagnosis, thereby avoiding unnecessary and often quite expensive diagnostic tests. Our proposed diagnostic work-up, which is specifically applicable to countries with limited diagnostic resources, is mainly guided by the clinical picture and more widely available laboratory tests. Clinicians should pay specific attention to the family history including consanguinity, occurrence of DM and the age of onset, the dysmorphic clinical features of genetic syndromes and of autoimmune diseases. Age of onset, race, use of medication, past medical history, and comorbidities are other factors giving direction to certain causes of severe insulin resistance. Also, compliance with treatment, daily insulin dose and self-assessed glucose levels should be questioned prior to classifying a patient as being severely insulin resistant.

A complete physical examination should include evaluation of body fat distribution (abnormal muscularity, and accumulation or lack of adipose tissue). Anthropometry (height, weight, and head circumference) including skinfold thickness measurement at various anatomic sites should be performed to objectively document lack or excess of body fat. If available, dual energy X-ray densitometry scans and whole body magnetic resonance imaging can be helpful to determine body fat distribution.
In countries with availability of diagnostic and financial resources, all patients with severe insulin resistance should undergo measurement of liver and kidney function, lipids (triglycerides and high-density lipoprotein cholesterol), glucose, insulin, HbA1c, and if available C-peptide. Cushing’s syndrome and acromegaly should be excluded by appropriate tests such as midnight serum cortisol measurement and IGF-1 level, respectively. Additional investigations such as anti-insulin autoantibodies, anti-insulin receptor antibodies, leptin, serum adiponectin, ACTH, or GH, should be carried out, if available. Serum adiponectin and leptin levels may distinguish lipodystrophy syndromes from IRS (types A and B). Serum adiponectin levels are typically high in IRS but are low in lipodystrophy syndromes (19, 38). Most patients with generalized lipodystrophies have (extremely) low levels of leptin (38), while leptin levels are often normal in IRS.

Table 4 and Table 5 provide an overview of the possible data obtained from medical history, physical examination and laboratory tests and the associated likelihood of the various causes of severe insulin resistance. The tables can guide the physician toward the likely cause of insulin resistance and start the best available treatment, also without genetic testing.

Table 4. Assessment of medical history in children with diabetes mellitus and severe insulin resistance

| Assessment               | Interpretation                                      |
|--------------------------|-----------------------------------------------------|
| Sex                      | Female: Type A IRS, type B IRS, acquired generalized and partial lipodystrophy |
|                          | Male: Type A IRS, type B IRS, acquired generalized and partial lipodystrophy |
| Race                     | Black: Type B IRS                                   |
| Age of presentation      | Shortly after birth: Donohue syndrome (= type A IRS), CGL |
|                          | Childhood: Rabson-Mendenhall syndrome (= type A IRS), CGL |
|                          | Puberty: Familial partial lipodystrophy            |
|                          | Adolescence: Type A IRS, Cushing’s syndrome, acquired generalized and partial lipodystrophy |
| Family history           | Insulin resistance: Type A IRS, CGL                |
|                          | Autoimmune disorders: Type B IRS, anti-insulin antibodies, acquired generalized and partial lipodystrophy |
| Consanguinity            | CGL                                                 |
| Past medical history     | Autoimmune background: Type B IRS, anti-insulin antibodies, acquired generalized and partial lipodystrophy |
| Spontaneous recovery     | Type B IRS                                           |
| Medication use           | Medication-related insulin resistance                |
| Oligomenorrhea, amenorrhea| Type A IRS, type B IRS, Cushing’s syndrome          |
|                          | Lipodystrophy                                       |

Table 5. Physical examination and laboratory findings in children with diabetes mellitus and severe insulin resistance

| Examination                  | Interpretation                                                                 |
|------------------------------|--------------------------------------------------------------------------------|
| Likeability to cause severe to extreme insulin resistance | Likely: Type A IRS, type B IRS, lipodystrophy, other genetic syndromes |
| Less likely                  | Acromegaly, Cushing’s syndrome, medication related insulin resistance, acquired partial lipodystrophy |
| Triglycerides                | Low to normal: Type A IRS, type B IRS                                         |
|                             | Elevated: Lipodystrophy, poorly controlled diabetes in general                 |
| Adiponectin                  | Low to normal: Lipodystrophy                                                  |
|                             | Elevated: Type A IRS, type B IRS                                              |
| Hormones                    | Elevated IGF-1, GH                                                              |
|                             | Elevated ACTH                                                                   |
|                             | Elevated cortisol                                                               |
| Acanthosis nigricans, hirsutism, hyperandrogenism | Type A IRS, type B IRS (characteristic distribution of acanthosis nigricans, involving perioral, perioral and labial regions), lipodystrophy |
| Cushingoid appearance (moon face, buffalo hump, striae, central fat distribution) | Cushing’s syndrome, familial partial lipodystrophy |
| Acromegaloid appearance     | Acromegaly, pseudo-acromegaly, lipodystrophy                                   |

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; IRS, insulin resistance syndrome.

Case Presentation—Part 2

Suriname does not have a pediatric endocrinology consultant or a clinical geneticist. Therefore, this very challenging case was extensively discussed with colleagues in The Netherlands. Annually, Dutch medical staff visit Suriname for special missions and training activities in order to keep health care knowledge up to date.

After treating the patient with high doses of subcutaneous insulin, she was started on several oral hypoglycemic agents alongside insulin. First, glibenclamide 5 mg twice daily was started. The dose was increased to 10 mg twice daily after 4 days. Since there was no glucose-lowering
effect, glibenclamide was discontinued after 1 month. In order to overcome the insulin resistance, intravenous insulin infusion was started in a dose of 0.07 IU/kg/day and gradually increased to 3.6 IU/kg/day, without a significant effect on blood glucose levels. She was restarted on a subcutaneous insulin schedule with intermediate acting insulin (Insulatard®) once daily and short acting insulin (Actrapid®) before each meal. Additionally, metformin was started in a dose of 500 mg twice daily, later increased to 1000 mg twice daily. Glibenclamide was restarted 2 weeks later in a dose of 10 mg once daily, later increased to 7.5 mg twice daily. None of these interventions had a significant effect on her blood glucose levels. She continued to have elevated glucose levels between 10 and 15 mmol/L (Fig. 2).

Due to limited diagnostic resources in Suriname, serum IGF-1, GH, ACTH, and C-peptide measurements, and islet cell autoantibodies or glutamic acid decarboxylase autoantibodies, could not be performed.

Karyotyping excluded Turner syndrome, investigated because of secondary amenorrhea and short stature. To identify signs of PCOS, a gynecologist was consulted. Transvaginal ultrasound showed normal anatomy of the female reproductive system, and ovaries with many antral follicles suspicious for PCOS, although there were no clinical signs of hyperandrogenism. She was treated with norethisterone 5 mg once daily for 10 days which resulted in a successfully induced withdrawal bleeding, after which regular menstrual cycles commenced.

All insulin injections were monitored or administered by trained nurses. Moreover, she was admitted to the pediatric intensive care unit for strict monitoring of treatment and sugar intake. Despite all these efforts, she continued to have hyperglycemia.

Nearly 2 months after admission, serum triglyceride levels were measured, which were elevated (Table 6). Because of an increased risk of acute pancreatitis, we started gemfibrozil 1200 mg daily, later increased to 2400 mg daily. Serum triglyceride levels effectively decreased, and gemfibrozil was ceased after 3 weeks.

Serology tests of HIV, Epstein–Barr, cytomegalovirus, and tuberculosis were all negative and leukocyte count and erythrocyte sedimentation rate was normal, making infectious causes of severe insulin resistance less likely. The combination of severe insulin resistance, hypertriglyceridemia and her typical physical features, after excluding other diagnoses as much as possible, suggested a diagnosis of CGL. On abdominal ultrasonography, a slightly enlarged liver was observed, without signs of hepatic steatosis. Echocardiography showed no signs of hypertrophic cardiomyopathy.

Nearly 4 months after admission, her DNA was sent to The Netherlands for genetic analysis to the University

### Table 6. Fasting biochemical blood results 2 months after admission

| Analyte                     | Value   | Reference range |
|-----------------------------|---------|-----------------|
| Albumin, g/L                | 40.8    | 32.0-56.0       |
| Triglycerides, mmol/L       | 7.12⁴   | 0.84-2.00       |
| Cholesterol, mmol/L         | 5.83⁴   | 0.00-5.20       |
| HDL cholesterol, mmol/L     | 1.0     | 0.8-1.4         |
| LDL cholesterol, mmol/L     | 3.41    | 0.00-3.88       |
| AST, IU/L                   | 19      | 0-38            |
| ALT, IU/L                   | 20      | 0-41            |
| LD, IU/L                    | 117     | 98-192          |
| Insulin, µIU/mL             | 20.2    | 9.3-29.1        |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low density lipoprotein; LD, lactate dehydrogenase.

³Value outside the reference range.

²LDL cholesterol level is less reliable due to elevated triglyceride levels.

⁴Insulin level was measured 12 hours after subcutaneous insulin administration.

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**Figure 2.** Course of various insulin doses, oral medication, and glucose levels during the 138-day admission period.
Medical Center Utrecht. DNA extraction kits (QIAAmp Blood Midi Kit, Qiagen Benelux) were provided to Suriname by the University Medical Centre of Groningen. Shortly thereafter, she was discharged while being on an intermediate acting insulin (Mixtard®), metformin, and glibenclamide. Due to complex social circumstances, she was transferred to a children’s home for further care.

In March 2020, 6 months after her initial admission, genetic analysis confirmed a homozygous known pathogenic variant in the AGPAT2 gene (AGPAT2 (NM_006412.4): c.[589-2A>G] [589-2A>G] p.[??][??]), confirming the diagnosis of CGL type 1 (Berardinelli–Seip syndrome, OMIM# 608594) (39). The variant was detected by targeted massively parallel/next generation sequencing (Illumina NGS) of the coding exons and flanking splice site sequences of 9 genes known to play a role in genetic lipodystrophies: AGPAT2, AKT2, BSCL2, CAV1, CAVIN 1, CIDEC, LMNA, PPARG, and ZMPSTE24. The coverage of this gene panel is >99% and no variants in the other genes mentioned were detected. The ClinVar database reports the AGPAT2 variant as pathogenic with a minor allele frequency in the Genome Aggregation Database (gnomADv3.1) of 0.0015 in subjects of African origin and it has been reported so far primarily in the African population. In fact, in our experience, most of the patients of African origin with CGL, type 1 have this variant either in homozygous state (as in our patient) or in compound heterozygous state with other pathogenic variants (40). This splice site variant, also known as IVS4-2A>G, potentially induces an aberrant splice site resulting in a frameshift and a premature termination at codon 228 (p.Val197Glufs*32).

## Lipodystrophies

### Definition and Classification

Lipodystrophies are a heterogeneous group of rare disorders that are characterized by selective loss of adipose tissue (31, 41). Although the exact incidence and prevalence are unknown, the prevalence of lipodystrophies is estimated at 1.3 to 4.7 cases per million (42).

We will describe the main subtypes of lipodystrophies. Subtypes including antiretroviral therapy-induced lipodystrophy in HIV-infected patients, progeroid syndromes, and autoinflammatory subtypes, will not be discussed in this article and we refer to previous publications by Brown et al. (36) and Bindlish et al. (37).

### Congenital Generalized Lipodystrophy (Berardinelli–Seip Syndrome)

CGL, or Berardinelli–Seip syndrome, is an autosomal recessive disorder characterized by near total absence of body fat since birth (32). The estimated prevalence is 1 in 1-10 million (43). Most patients are born to consanguineous parents (39, 40, 44-46). The syndrome is characterized by a generalized absence of adipose tissue from birth or soon thereafter. Physically, muscular hypertrophy, an acromegaloid appearance, umbilical prominence, hirsutism, and acanthosis nigricans may be present. Additionally, common features include hepatomegaly, NAFLD, hypertriglyceridemia, polycystic ovaries, cardiomyopathy, and severe insulin resistance (32).

CGL is most commonly caused by pathogenic variants in acylglycerol phosphate acyltransferase 2 or AGPAT2 gene (CGL, type 1)(OMIM# 608594) (39) or Berardinelli–Seip Congenital Lipodystrophy 2 or BSCL2 gene (CGL, type 2) (OMIM# 269700) (45). AGPAT2 enzyme catalyzes conversion of 1-acylglycerol-3-phosphate (also known as lysophosphatidic acid) to 1,2 diacylglycerol-3-phosphate (known as phosphatidic acid) by esterifying a fatty acyl group at the sn-2 position of the glycerol backbone during the biosynthesis of triglycerides and other phospholipids (47). The BSCL2 gene encodes a protein named seipin, which plays an important role in lipid droplet fusion and adipogenesis (48-50). The other extremely rare CGL subtypes are type 3, which is due to biallelic variants in caveolin 1 (CAV1) gene (OMIM# 612526) (51) and type 4, which is due to variants in caveolin associated protein 1 (CAVIN1) gene (OMIM# 613327), previously known as polymerase I and transcript release factor (PTRF) (52). Caveolin 1 is a major component of caveolae, specialized plasma membrane microdomains appearing as 50 to 100 nm vesicular invaginations, which are involved in maintaining the integrity and function of the lipid droplets and in transport and/or storage of fatty acids and cholesterol (53). Caveolae associated protein 1 also plays a role in the biogenesis of caveolae and co-localizes with caveolin 1 in adipocytes (54).

There are phenotypic differences between the 4 subtypes of CGL (36, 37). Insulin resistance and subsequent DM and hypertriglyceridemia often present in adolescence. Fertility is commonly reduced in females. Fertility may also be reduced in males with CGL2 and CGL4, since teratozoospermia has been reported in a male patient with CGL2 (55) and reduced spermatids in a young male with CGL4 (56).

CGL, type 1 patients have selective absence of metabolically active adipose tissue located in most of the subcutaneous, intra-abdominal, intrathoracic regions and in bone marrow but preservation of mechanical adipose tissue located in the palms, soles, under the scalp, orbital, peri-articular regions, perineum, vulva, and pericapsular regions of the kidneys (57). CGL, type 2 patients lack both metabolically active and mechanical body fat (58), have mild cognitive impairment, and a cardiomyopathy
A single female patient with CGL, type 3 had extremely little body fat, short stature, and vitamin D resistance. CGL, type 4 patients have extremely little body fat, congenital myopathy, high serum creatinine kinase levels, pyloric stenosis, and cardiomyopathy. Although the exact pathophysiology of metabolic complications in CGL is unknown, animal models of CGL also develop diabetes, hepatic steatosis, and dyslipidemia. Adipocyte function includes storage of triglycerides and production of hormones and cytokines, such as leptin and adiponectin. The lack of adipose tissue results in a reduction of its functional capacity. Hence, fatty acids are stored as triglycerides in other tissues, such as the liver and muscle causing hepatic steatosis and peripheral insulin resistance. Low levels of serum leptin can induce hyperphagia and exacerbate metabolic complications of insulin resistance. Metabolic complications are related to the extent of fat loss. Other comorbidities that are associated with insulin resistance include reproductive dysfunction (PCOS, oligomenorrhea, reduced fertility) and NAFLD.

**Diagnosis**

Although there are no clear diagnostic criteria for lipodystrophy, the diagnosis can often be suspected based on the clinical picture, including medical history, physical examination, body composition, and laboratory findings such as serum triglycerides, without the need for genetic testing.

Physical characteristics, metabolic complications, and organ abnormalities that are associated and can help to identify a patient with lipodystrophy are listed in Table 7.

The near total lack of body fat and prominent musculature in our patient suggested the diagnosis of CGL. She also had premature onset of DM, hypertriglyceridemia, acanthosis nigricans, and mild hepatomegaly. Interestingly, the ultrasound examination of abdomen did not reveal evidence of hepatic steatosis. However, the sensitivity of ultrasound is not that good compared with magnetic resonance imaging or $^1$H-spectroscopy–based methods to quantify hepatic fat. Lack of myopathy and a normal serum creatine kinase level excluded the diagnosis of CGL, type 4. Furthermore, lack of intellectual impairment and cardiomyopathy and preservation of subcutaneous adipose tissue in the palms and soles suggested CGL, type 1 instead of CGL, type 2. Molecular genetic testing in our patient confirmed the diagnosis of CGL, type 1.

**Management of Lipodystrophy**

Treatment of lipodystrophy syndromes is supportive and aimed at treating the metabolic abnormalities, thereby preventing short- and long-term complications of the disease.

**Nutritional and Lifestyle Management**

The most important factors in managing lipodystrophy are dietary and physical exercise. Patients should adhere to a balanced diet, including 50% to 60% carbohydrates,
20% to 30% fat, and 20% protein. For patients with severe hypertriglyceridemia and especially those with chylomicronemia (serum triglycerides exceeding 1000 mg/dL or 11.3 mmol/L), extremely low-fat diet with <15% of total energy as fat should be advised. Restriction of total energy is helpful to manage metabolic complications, but it is often difficult as hypooleptinemia stimulates appetite and hyperphagia. Increased physical activity should be recommended, unless contraindicated due to concurrent morbidity, such as cardiomyopathy.

Hypertriglyceridemia

Lipid lowering drugs could be considered in children and adolescents with lipodystrophy and severe hypertriglyceridemia. The risk of acute pancreatitis is higher with serum triglyceride levels exceeding 1000 mg/dL (11.3 mmol/L) (64). In patients with triglyceride levels higher than 500 mg/dL, fibrates such as gemfibrozil or fenofibrate can be used to reduce the risk of acute pancreatitis. However, safety and effectiveness data of fibrates in the pediatric population are scarce. Important adverse effects of fibrates are myopathy and rarely rhabdomyolysis, especially when used together with statins. High doses of long chain highly polyunsaturated omega-3 fatty acids from fish oil, such as eicosapentaenoic and docosahexaenoic acids, can be used to lower serum triglycerides.

Leptin Replacement Therapy

Metreleptin is a recombinant analogue of leptin and is indicated as replacement therapy, in addition to diet and lifestyle modifications, in patients with generalized (both congenital and acquired) lipodystrophy (65). Metreleptin is approved for generalized lipodystrophies in the United States, but for both generalized and partial lipodystrophies in Japan and Europe. A study by Brown et al. assessed the efficacy of metreleptin in a pediatric cohort of 53 children and showed that metreleptin significantly reduced blood HbA1c, serum C-peptide, and triglyceride levels, especially in adolescent patients (66). In this cohort, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels also decreased, suggesting a positive effect on hepatocellular damage. In a subgroup of 17 patients who underwent liver biopsies, the histologic NAFLD activity score decreased, which could indicate that metreleptin could help prevent worsening of NAFLD to liver cirrhosis. Moreover, after 1 year of metreleptin treatment, the proportion of patients requiring insulin dropped from 45% to 23%, suggesting an improvement of insulin sensitivity (67). Metreleptin is well tolerated and side effects include injection site reactions, hypoglycemia, and development of neutralizing antibodies to metreleptin. The precise clinical significance of the neutralizing antibodies remains unclear.

Follow-up

Children with CGL should be screened for diabetes, dyslipidemia, NAFLD, reproductive dysfunction, cardiovascular disease, and kidney disease. Details on the recommendations with regards to the frequency and extent of this screening are out of the scope of this article and can be found in the article of Brown et al. (66).

Case Presentation—Part 3

Currently, the patient has stable blood glucose levels with glibenclamide 7.5 mg twice daily and metformin 1000 mg twice daily. Her most recent serum triglycerides (0.82 mmol/L), cholesterol (3.36 mmol/L), AST (22 IU/L), and ALT (32 IU/L) were in the normal range. She does not have diabetic retinopathy or nephropathy.

Treatment with metreleptin has not been started because of a lack of availability and insurance coverage in Suriname. We are investigating the possibilities to obtain this therapy from The Netherlands.

Discussion

We presented a case of a teenage girl with severe insulin resistance who was diagnosed with CGL type 1. The current case is an excellent example of how the correct diagnosis can be reached after clinical assessment including a thorough review of medical history, a careful physical examination and basic laboratory investigations. We provide a systematic approach to the differential diagnosis and work-up to clinically diagnose a child with insulin-resistant DM. Genetic testing was performed to confirm our clinical diagnosis, but was not essential to reach the diagnosis. While distinction between various subtypes of CGL can be made based on clinical features and physical examination, such distinction is quite difficult to make for patients presenting with familial partial lipodystrophy. In case a clinical diagnosis cannot be established, the view of the clinician remains of utmost importance to direct genetic testing. This is not only the case in low- or middle-income countries, but also in high-income countries. Furthermore, as novel genotype-specific therapies are discovered, genetic testing may guide therapy. Lastly, our case underlines the importance of international collaboration and establishment of both regional and global centers of excellence for diagnosing and treating patients with rare diseases. The European Consortium of Lipodystrophies (ECLip) and the Lipodystrophy Laboratory at UT Southwestern are examples of such international collaborations.
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Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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