Congenital Generalized Lipodystrophy 3 & 4 Presenting as Pancreatitis

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PRESENTATION OF CASE

A 7 years child presented with abdominal pain of 3 days duration in epigastric region (radiating to the back, aggravated with food, and relieved partially on bending forward), abdominal distension, non-bilious vomiting, dyspnoea and altered sensorium. Systemic examination revealed hepatomegaly, tachypnoea, bilateral intercostal retractions and hypovolemic shock.

There was no significant past history that is relevant to the present case scenario. There was history of voracious appetite. Also, child had exercise intolerance and cannot cope up with his peers in physical activity. There was no significant family history. The child was born to consanguineous couple. He was born at 40 weeks of gestation and had not cried immediately after birth and had history of neonatal convulsions and used antiepileptics for one month and later stopped. No further convulsions since then. Developmental milestones were appropriate for age.

General examination revealed lipoatrophy, muscular hypertrophy, acromegaloidism, acanthosis nigricans and hypertrichosis. Clinically diagnosed as acute pancreatitis. Biochemical evaluation revealed elevated amylase and lipase suggestive of pancreatitis. Also found hyperglycaemia. Managed with fluid boluses, inotropes, octreotide, intravenous antibiotics and metformin. Hypertriglyceridemia was found while evaluating aetiology of pancreatitis. Ultrasound abdomen revealed changes suggestive of pancreatitis, ascites and altered hepatic echotexture. Magnetic resonance imaging showed pancreatic pseudocyst of size 10 x 9 cm. Hormonal evaluation revealed low levels of leptin suggestive of lipodystrophy. Genetic analysis confirmed the diagnosis of congenital generalized lipodystrophy 3&4. Child's height was 116 cm (between 10th and 25th percentile), weight was 19 kg (between 10th - 25th percentile), and body mass index (BMI) was between 25 - 50th percentile. child had complete absence of subcutaneous fat over trunk, limbs and face and muscular hypertrophy (figure 1), severe acanthosis nigricans over fingers, toes, axillae and groin, phlebomegaly (figure 2). Child also had hypertrichosis, prominent orbital ridges, prognathism and acromegaloidism (figure 3). Genitals were normal. Musculoskeletal examination displayed good power in the extremities. Muscle stretch reflexes were normal. He was able to stand and ambulate independently. Joint examination was normal.

Child was in altered sensorium and tachypnoeic at time of admission. He was afebrile at admission. Patient was kept in paediatric intensive care unit at the time of admission. Systemic examination revealed bilateral lower intercostal retractions, bilateral crepitations, hepatomegaly and hypovolemic shock. Clinically diagnosed as acute pancreatitis with multisystem involvement and treated with fluid boluses for management of hypovolemic shock followed by inotropes, octreotide and intravenous antibiotics. Patient general condition improved over 3 days with regaining of sensorium, decreased respiratory rate and became normotensive and transferred to paediatric ward for further evaluation and management.

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Biochemical evaluation revealed elevated serum amylase and lipase suggestive of pancreatitis, normal renal parameters, normal hepatic parameters. Fasting plasma glucose and postprandial plasma glucose were in diabetic range (table 2). As the patient developed Diabetes Mellitus, we started him on oral anti diabetic agents with Metformin which is an Insulin sensitizer. Patient developed euglycemic status with metformin during follow up. We evaluated for causes of pancreatitis in child. We did lipid profile as advised by gastroenterologist which showed hypertriglyceridemia (table 3). According to American academy of paediatrics (AAP) and American Heart Association (AHA) the normal triglyceride levels in children between 0 to 9 years of age are as follows. Acceptable levels are <75 mg/dl, borderline levels are 75 to 99 mg/dl and high levels are >100 mg/dl. Hypertriglyceridemia with levels more than >500 mg/dl or >1000 mg/dl in adults are usually associated with pancreatitis. Probably levels of triglycerides >100 mg/dl in children may be toxic to pancreas resulting in pancreatitis. In our patient the triglyceride levels were 240 mg/dl. Hormonal evaluation revealed low levels of leptin (table 3), which is produced exclusively by adipose tissue suggestive of lipodystrophy.

Ultrasound abdomen revealed acute pancreatitis changes, moderate ascites with altered hepatic echotexture. Magnetic Resonance imaging (MRI) abdomen revealed large pancreatic cystic space occupying lesion with T2 hyper signal intensity measuring 10×9 cm. Multiple solid internal component with T2 and T1 hyposignal intensities. There was marked absence of all fat depots including gluteal fat with preservation of marrow fat and lipid filled Liver favouring lipodystrophy (figure 4). Chest x-ray revealed right sided pleural effusion. Complete blood picture showed neutrophilic leucocytosis, thrombocytosis. Peripheral smear examination was normal. 2-dimensional echocardiography showed no evidence of hypertrophic cardiomyopathy or cardiac enlargement. So, we got genetic analysis done (Table 1) which revealed congenital generalized lipodystrophy 3 & 4 with mutation in CAV1 (Caveolin 1) and PTRF (polymerase 1 and transcript release factor) mutations respectively.

CLINICAL DIAGNOSIS

Pancreatitis with Multisystem Involvement

DIFFERENTIAL DIAGNOSIS

In an Infant

1. Short syndrome: slit lamp examination, short stature.
2. Neonatal progeroid syndrome: prominent veins over scalp, premature teeth, peudohydrocephaloid appearance.
3. Lysosomal storage disorders like Gaucher's disease, Krabbe disease.
4. Russell diencephalic syndrome: MRI brain.

In a Child

1. Dunnigan lipodystrophy spares the face, cushingoid appearance, mutation in lamina gene
2. Rabson-Mendenhall syndrome: insulin resistance syndrome
3. Insulin dependent diabetes mellitus

In an Adult

1. Barraquer –Simons syndrome: asymmetric.
2. Acquired Immunodeficiency Deficiency Syndrome (AIDS) associated lipodystrophy.
3. Partial lipodystrophy.
4. Lawrence syndrome.

Figure 1. Lipoatrophy with Muscular Hypertrophy

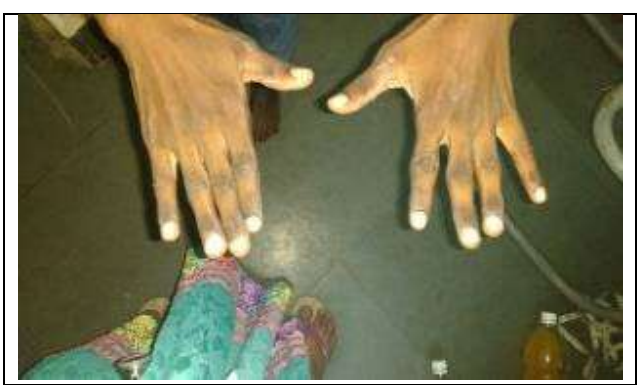

Figure 2. Phlebomegaly

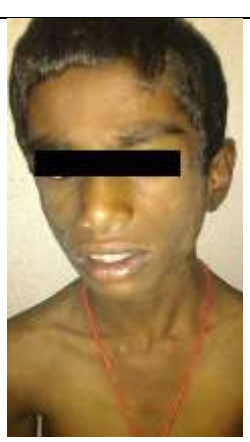

Figure 3. Acromegaloidism

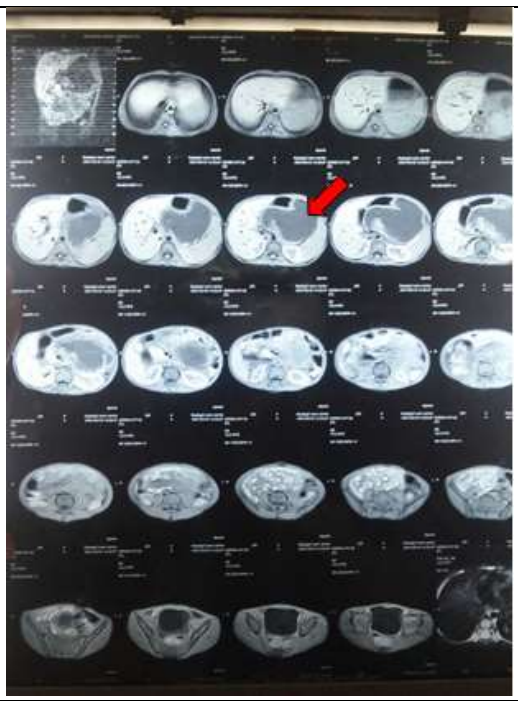

Figure 4

Figure 4 shows revealed large pancreatic cystic space occupying lesion with T2 hyper signal intensity measuring 10×9 cm. multiple solid internal component with T2 and T1 hyposignal intensities, marked absence of all fat depots including gluteal fat with preservation of marrow fat and a lipid-filled liver.

PATHOLOGICAL DISCUSSION

Test	Results	Reference Range
CGL1-AGPAT2	Not Detected	Not Detected
CGL2-BSCL2	Not Detected	Not Detected
CGL3-CAV1- EXON 01	Not Detected	Not Detected
CAV1- EXON 02	Detected	Not Detected
CAV1- EXON 03	Not Detected	Not Detected
CGL4- PTRF- EXON 1.1	Detected	Not Detected
PTRF- EXON 1.2	Detected	Not Detected
PTRF- EXON 2.1	Detected	Not Detected
PTRF- EXON 2.2	Not Detected	Not Detected

Table 1. Genetic Analysis by Real Time Polymerase Chain Reaction

Parameter	Result
Serum amylase	1180 IU/Ml
Serum lipase	1276 IU/mL
Fasting blood sugar	128 mg/dl
Postprandial blood sugar	230 mg/dl
Blood urea	28 mg/dl
Serum creatinine	0.6 mg/dl
Serum total cholesterol	155 mg/dl
Serum triglycerides	240 mg/dl
Serum HDL	22 mg/dl
Serum VLDL	48 mg/dl
Serum total bilirubin	0.8 mg/dl
Direct bilirubin	0.2 mg/dl
Indirect bilirubin	0.6 mg/dl
SGOT	35 IU/L
SGPT	17 IU/L
ALP	155 IU/L
Serum leptin	0.41 units (normal 2 to 3 units)
HbA1c	6.53%
Serum sodium	136 meq/L
Serum potassium	4.5 meq/L
Serum chlorides	101 meq/L
Serum calcium	8.5 mg/dl
Serum insulin	2.5 micro IU/ml

Table 2. Biochemical and Hormonal Parameters

DISCUSSION

Lipodystrophy is a disorder of the lipid and carbohydrate metabolism clinically characterized by varying levels of fat loss in adipose tissues. Congenital Generalized Lipodystrophy (CGL), also known as Berardinelli-Seip lipodystrophy (BSCL), was first described in 1954 by Berardinell[1] and later reviewed by Seip in 1959.[2] It has an autosomal recessive inheritance. It is a rare disorder with a prevalence of less than one case per 12 million individuals.[3] So far 120 cases have been described worldwide according to Garg.[3]

Lipodystrophy is characterized by a near complete lack of adipose tissue from birth and, later in life, the development of metabolic complications, such as diabetes mellitus, hypertriglyceridemia and hepatic steatosis.

Adipose cells are scarce and have a low volume due to the fact that they are unable to store lipids. Insulin resistance may develop into diabetes mellitus. Most affected individuals also have hypertriglyceridemia, which can lead to eruptive xanthomas and pancreatitis and hepatic steatosis.

Children with congenital generalized lipodystrophy have a distinctive physical appearance. This disease is clinically characterized by loss of subcutaneous adipose tissue, muscular hypertrophy, acromegalic appearance, accelerated growth, hypertrophic cardiomyopathy[4] and hepatosplenomegaly. Our patient had characteristic phenotype with generalized lipoatrophy with muscular hypertrophy. Morphological and functional study of skeletal musculature suggests increased muscle mass results from hyperplasia rather than hypertrophy.[5]

Many people with this disorder develop acanthosis nigricans due to peripheral insulin resistance.[6] Our patient had severe acanthosis nigricans involving nape of neck, axilla, groin, dorsum of hands and feet. Dyslipidemia observed in our patient were hypertriglyceridemia with low levels of high-density lipoprotein (HDL). Major defect in lipid metabolism lies in inability of adipocytes to store fat, probably due to abnormal functioning of glucose transporters (GLUT) 1-7 found in skeletal muscle, adipose tissue and cardiac muscle. As a result, intracellular levels of glycerol are low, hampering storage of free fatty acids into triglycerides.

Hepatomegaly observed in our patient may be due to triglyceride and glycogen accumulation in hepatocytes. These patients may develop cirrhosis as a part of long-term complication of lipodystrophy. Hypermetabolism characterized by voracious appetite and hyperhidrosis is seen in some patients. This is possibly due to increase in active peroxisomes and mitochondrial defects of hepatocytes and myocytes, to utilize excess energy that is

not stored as fat. Our patient had voracious appetite but still lean probably due to hypermetabolism as said above.

The clinical diagnosis of congenital generalized lipodystrophy (CGL) is based on major criteria and minor criteria. Three are five major criteria and six minor criteria. Of these, three major criteria or two major plus two minor criteria make the diagnosis of Berardinelli–Seip lipodystrophy (BSCL) likely. Major criteria are lipoatrophy affecting the trunk, limbs, and face, acromegaloid features, hepatomegaly, hypertriglyceridemia, and insulin resistance. Minor criteria are hypertrophic cardiomyopathy, psychomotor retardation, hypertrichosis, precocious puberty in females, bone cysts and phlebomegaly.

Of these criteria, our patient had all five major criteria that includes lipoatrophy, acromegaloidism, hypertriglyceridemia, insulin resistance and hepatomegaly and two minor criteria that includes phlebomegaly and hypertrichosis which made the possibility of congenital genital lipodystrophy likely and biochemical evaluation revealed patient had low levels of leptin levels, which is produced exclusively by adipose tissue confirming our diagnosis and finally, genetic analysis further confirmed our diagnosis of congenital lipodystrophy type 3& 4. Gene for congenital generalized lipodystrophy maps to chromosome 9q34 and 11q13[7,8] for type 1 and type 2 CGL respectively. There are four types of congenital generalized lipodystrophy. Type 1, type 2, type 3 and type 4.

Type 1CGL**:** In individuals with Type 1 CGL, the disorder is caused by a mutation at the AGPAT2 (acyl glycerol 3 phosphate o - acyltransferase 2) gene which encodes for enzyme which is important in the biosynthesis of fats. This enzyme is highly expressed in adipose tissue, so lipids cannot be stored in the adipose tissue. Individuals with CGL type 1 lack metabolically active fat, which is the fat plays a role in the storage and release of energy and is located in subcutaneous regions, intermuscular regions, the bone marrow and areas within the abdomen and chest, but mechanical fat is well preserved. Mechanical fat is the fat that supports and protects regions subjected to mechanical insults and is located in the palms, soles, orbits, scalp, and around the joints.

Type 2 CGL: In those who have Type 2 CGL, a mutation in the BSCL2 gene encoding the Seipin. Expression of mRNA for Seipin Protein is low in adipose tissue, but high in brain. They have higher incidence of mental retardation and mechanically active adipose tissue is absent in these patients. They have lower levels of leptin and these patients present with early onset of diabetes mellitus.

Type 3 CGL: Type 3 CGL involves a mutation is caused by a mutation in the CAV1 gene. This gene codes for the Caveolin protein, which is a scaffolding membrane protein. This protein plays a role in lipid regulation. High levels of Cav1 are normally expressed in adipocytes. Thus, when the CAV1 gene mutates the adipocytes do not have Cav1 and are unable to properly regulate lipid levels.

Type 4 CGL: A mutation in the PTRF (polymerase 1 and transcript release factor) gene causes Type 4 CGL. One of the roles the PTRF product has it to stabilize and aid information of caveolae. So caveolae are unable to form properly and unable to perform their role in the regulation of lipids. So, Type 3 and type 4 have a common defect in the regulation of lipid.

DISCUSSION OF MANAGEMENT

The treatment of lipodystrophy is directed towards the specific symptoms that are apparent in each individual. All patients should restrict their total energy intake, as well as intake of saturated fats and simple carbohydrates and replace them with complex carbohydrates, soluble fibres, medium chain triglycerides and unsaturated fatty acids. All patients must do regular exercise to prevent development of diabetes mellitus. If the patient develops diabetes mellitus as in our case, manage with either oral hypoglycaemic agents like metformin and thiazolidinediones which are insulin sensitizers or insulin if there is no response to oral antidiabetic agents. In our patient we managed with metformin and patient achieved euglycemic status patient with metformin alone. There are many case reports in the literature which required insulin.

Lipodystrophy is associated with hypertriglyceridemia, which may be treated with fibric acid derivatives, statins, or omega 3 fatty acids. Our patient had pancreatitis with pancreatic pseudocyst formation probably due to hypertriglyceridemia. However, patient improved with symptomatic treatment of pancreatitis. We did not give him either fibric acid derivative or statins. Metformin we have given for the management of diabetes mellitus might have showed favourable response on lipid profile also.

Severe lipodystrophy is sometimes associated with leptin deficiency. United States Food and Drug Administration (USFDA) approved Myalept. Myalept is a brand name for metreleptin injection. Metreleptin injection is used as an adjuvant to diet to treat complications of leptin deficiency in patients with both congenital and acquired generalised lipodystrophy. Myalept is a recombinant analogue of human leptin and is taken once a day, same time by subcutaneous injection. The initial dose of metreleptin injection is 0.06 mg per kg per day and gradually titrated up to a maximum dose of 0.13 mg per kg per day. It has been found to be beneficial for improving metabolic complications, such as diabetes and hypertriglyceridemia.[9] Finally, in some cases, patients may develop chronic liver disease which ultimately require a liver transplantation. To the best of our knowledge, ours is the first case which showed congenital generalized lipodystrophy with pancreatitis with pseudocyst formation.

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