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Case Report (Pages: 4275-4284)

Congenital Generalized Lipodystrophy in a Youth Presented with Sclerotic and Lytic Bone Lesions; a Family with AGPAT2 Mutation

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Abstract

Background

Congenital generalized lipodystrophy (CGL) is a rare disease. It is associated with near total fat loss, severe insulin resistance and hypoleptinemia leading to metabolic derangements.

Case Presentation

We report a 25- year- old female with 1-Acylglycerol-3-phosphate-O-acyltransferase 2 (APGAT2) mutation, and both sclerotic and lytic bone lesions together for the first time. Bone cyst is one of the manifestations of CGL with AGPAT2 mutation. Patients usually have sclerotic bone lesions before and lytic bone lesions after puberty. Our patient had lytic bone lesions in (femur) long bones and also sclerotic lesions in the pelvic which was related to AGPAT2 mutation.

Conclusion

The young female had acral enlargement, hepatomegaly and both sclerotic and cystic bone lesions with AGPAT2 mutation.

***Key Words*:** AGPAT2 mutation, Congenital generalized lipodystrophy, Cystic bone lesions.

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1- INTRODUCTION

Lipodystrophy is a group of heterogeneous conditions with partial or complete loss of adipose tissue. It may be congenital or acquired. Based on these characteristics four subgroups are identified: Congenital generalized lipodystrophy (CGL), Acquired generalized lipodystrophy (AGL), Familial partial lipodystrophy (FPL), and Acquired partial lipodystrophy (APL) (1, 2).

Congenital generalized lipodystrophy or Berardinelli-Seip syndrome is a rare genetic autosomal recessive disorder with a prevalence of 1 in 10 million people (3). About 300 patients have been described in the literature as having lipodystrophy (4, 5). Due to the fat loss and muscular nature of the disease, it is diagnosed at birth and throughout the first year of life. Some patients, however, may be diagnosed in adulthood (6). According to Magnetic resonance imaging (MRI) and autopsy inspection, although subcutaneous fat is absent in intra-abdominal, intra-thoracic, limbs and bone marrow, it is preserved in the orbits, tongue, scalp, perineum, palms, soles, and periarticular region. White adipose tissue is divided into two sub groups: 1) Adipose tissue with metabolic activity which is missing in Congenital generalized lipodystrophy1 (CGL1) and Berardinelli-Seip congenital lipodystrophy type 2 (BSCL2), 2) Mechanical adipose tissue which is maintained in CGL1 and absent in BSCL2 (7).

Patients with lipodystrophy experience several metabolic complications that display the important endocrine role of adipose tissue (1). Up to now four genetic mutations have been described: CGL1: 1-acylglycerol-3-phosphate-*O*-acyltransferase 2 (AGPAT2), CGL2: Berardinelli-Seip congenital lipodystrophy type 2 (BSCL2), CGL3: caveolin-1 (CAV1), CGL4: polymerase I and transcript release factor (PTRAF) (8). CGL1 and CGL2 account for about 95% of cases. CGL2 is more severe than CGL1 (9, 10). CGL2 associated with near total fat loss, severe insulin resistance and hyperleptinemia leading to diabetes, hypertriglyceridemia, steatohepatitis, hyperandrogenism and anovulation (6, 11). AGPAT2 mutation has sometimes been accompanied by sclerotic bone lesions before and lytic bone lesions after puberty. In some patients, patchy sclerotic lesions after puberty have been also seen (12).

The conventional treatment can be used for metabolic disorders. However, in severe cases they may fail to control metabolic derangement. In these conditions leptin therapy is beneficial, especially in severe insulin resistance and steatohepatitis. Recombinant leptin such as metreleptin, has been approved as a therapeutic agent by the Food and Drug Administration *(*FDA*)* since February 2014 (5, 6, 13). Here we report a 25- year- old female with acral enlargement, hepatomegaly and both sclerotic and cystic bone lesions with AGPAT2 mutation. Also, informed consent was obtained from all participants included in the study.

2- CASE PRESENTATION

A 25- year- old female patient was referred to the endocrinology department with acral enlargement, hepatomegaly together with sclerotic and cystic bone lesions (**Figure.1**). In the history, she was full-term at birth with weight and height of 2.5 kg and 50 cm, respectively. During childhood, she was muscular and taller than her classmates. At ten years of age, she began noticing the skin on her neck and axillary region looked dark and acanthosis nigricans was confirmed by a dermatologist. Further clinical evaluation

detected diabetes and hypertriglyceridemia. Therefore, Metformin and Gemfibrozil were prescribed. Despite premature the larche and adrenarche, she was reported to have primary amenorrhea at the age of 16 years old. Laboratory-based testing confirmed acromegaly. Accordingly, dynamic pituitary Magnetic resonance imaging (MRI) detected no sign of pituitary adenoma. Her insulin like growth factor-1 (IGF1) and growth hormone (GH) inhibitory test by glucose were normal eight years ago and repeated tests had the same results (**Table.1**).

She had the history of several surgeries: adenoidectomy and tonsillectomy, salivary gland stone removal and umbilical hernia repair. Recently, she had abdominal pain while doing physical activity by abdominopelvic computed tomography scan (CT scan) detected sclerotic bone lesions in pelvic and cystic lesions in the femur (**Figure.2**).

Also, severe fatty liver infiltration, mildly enlarged spleen and abdominal fat loss were evident. Bioimpedance analysis was performed as an alternative way to recognize fat mass. The findings are presented in **Table.2**. On abdominopelvic ultrasound (US) the right and left kidney sizes were 142*46 mm and 133*63 mm, respectively. Extensive debris within bladder was seen. Echocardiography was normal and a negative Human immunodeficiency virus (HIV) test result was shown. A description of her last laboratory test is listed in **Table.3**.
Due to acromegaloid facial features, after treatment and pain relief, she was referred to our department for more evaluation. In the family, her grandfather had a similar appearance. Based on history, gene accumulation was strong. Male siblings 1 and 2 (patient 2 and 3), had athletic appearance (look like a person who is physically fit) and male sibling 2 (patient 3) had acanthosis nigricans, too. Based on history and physical examinations, the patient was suspected with congenital generalized lipodystrophy and genetic experiment was performed to confirm the diagnosis. The entire coding sequence of AGPAT2 gene was screened for the presence of mutation using polymerase chain reaction (PCR) followed by direct sequencing (Primer sequences are available on request). A heterozygous indel mutation (rs145169122, NM_001012727.1:c.*217_*218insGGCT CG) was detected in index patient (**Figure.3**). The index patient was homozygote and her parents and a sibling were heterozygote (**Figure.4**).

Several other polymorphisms were also detected including (rs10320, rs6951), in patient 2 and rs488019 in patient 3 and both parents. Interestingly, despite having athletic appearance, high levels of insulin and triglyceride levels and mild to moderate fatty liver (grade1-2) on US patient (2), was not a carrier of AGPAT2 mutation. On the other hand, patient (3), with athletic appearance, Acanthosis nigricans, but normal serum insulin level and no fatty liver on US was heterozygous for AGPAT2 mutation.

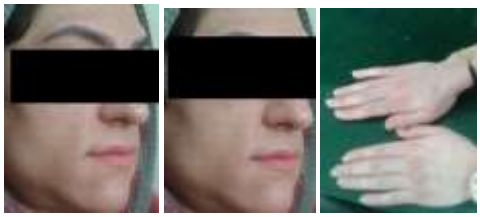

Fig.1: Prognathism, prominent orbital ridges (A, B) acral enlargement (C).

Table-1: Index case laboratory test

Laboratory test : 2002	Normal range	Index patient	Laboratory test : 2007	Normal range	Index patient
FBS (mg/dl)		184	FBS (mg/dl)		95
Triglyceride (mg/dl)	<200	662	Triglyceride (mg/dl)	<200	479
AST (IU/L)	UP to 40	70	AST (IU/L)	UP to 40	74
ALT (IU/L)	UP to 40	72	ALT (IU/L)	UP to 40	62
IGF1 (ng/ml)	286-660	694	IGF1 (ng/ml)	240-506	222
GH 1 h after 75 gr glc (ng/ml)	<1	2.2	GH 1 h after 75 gr glc (ng/ml)	<1	0.4
Prolactin (ng/ml)	Up to 20	2.2	Prolactin (ng/ml)	Up to 20	6.4
T4 (mic/dl)	4-12	10.7	Cholesterol (mg/dl)	<200	150
TSH(mIU/l)	0.5-5.5	1.4	Viral markers for hepatitis		Negative
Insulin (micU/ml)	2.6-25	>70	LH (mIU/ml)		1.5
Cortisol (µG/dl)		8	FSH (mIU/ml)		4.4
			Estradiol (pg/ml)		39.5

FBS: Fasting blood sugar; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; IGF1: Insulin-like growth factor 1; GH: Growth Hormone; T4: Thyroxine; TSH: Thyroid-Stimulating Hormone.

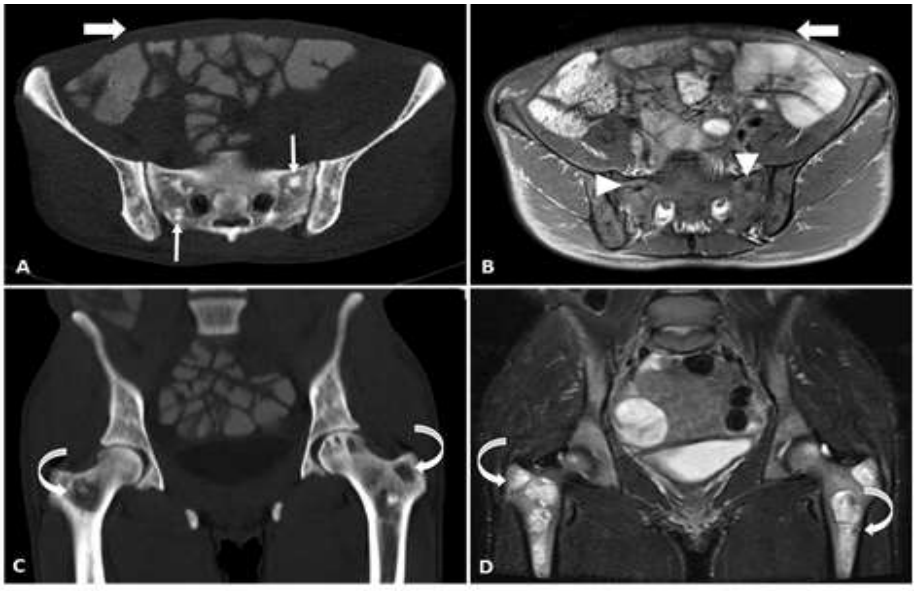

Fig.2: Imaging findings of the patient. Sclerotic bony lesions (arrows) in axial CT scan (A) with corresponding hypointense foci (arrow heads) in T1-weighted MRI (B) of the pelvis. Considerable loss of subcutaneous fat is also noted (thick arrows). There are well-defined cystic appearing lytic lesions in coronal CT scan (C) and T2-weighted MRI (D) of proximal femurs (curved arrows).

Table-2: Body composition analysis of the index patient and her family members

Variables	Index case	Mother	Father	Brother 1	Brother 2
Age (year)	25	45	53	30	28
Weight (Kg)	62.8	79.9	76.2	97.8	88.6
Height (cm)	165	163	176	189	194
BMI (Kg/m^2)	23.1	30.1	24.6	27.4	23.5
Total fat (%)	16.9	33.6	25.4	21	14
Visceral fat rating desirable range total fat (%)	21-23	23-34	11-22	8-20	8-20
Fat mass (Kg)	10.6	26.8	19.4	20.5	12.4
Visceral fat rating desirable range Fat mass(Kg)	-	-	7-16	6.7-19.3	6.6-19.1
FFM (Kg)	52.2	53.1	56.9	77.3	76.2
TBW (Kg)	38.2	38.9	-	-	-

BMI: Body Mass Index; FFM: Fat Free Mass; TBW: Total Body Water.

Table-3: Last laboratory values of family members and the index patient

Variables	Normal range	Index patient	Father	Mother	Patient 2	Patient 3
Age, (Year)		25	53	45	30	28
WBC×10^9/L	4-10	7.6	8.16	7.4	5.28	5.6
Hemoglobin, (mg/dl)		10.8	15.9	15.3	16.6	18.4
MCV	80-96	94	93	87	87	89
Platelet×10^9/L	150-450	169	236	260	193	163
Urea, (mg/dl)	<50	20	25	18	23	31
Creatinine (mg/dl)	<1.5	1	1.08	0.8	1.3	1.12
Na, (mEq/L)	135-145	142	142	140	145	143
K, (mEq/L)	3.5-5.1	4	4.8	4.3	4.8	4.5
Calcium (mg/dl)	8.5-10.3	9.1	9.4	9	9.7	9.7
Phosphorus, (mg/dl)	2.7-4.5	3.8	3.1	3.1	4.7	3.2
ALKP, (U/L)	64-306 F 80-306M	93	213	119	172	175
AST, (U/L)	UP to 40	19	19	13	24	22
ALT, (U/L)	UP to 40	25	17	17	49	25
Triglyceride, (mg/dl)	<200	633	266	237	393	108
Cholesterol (mg/dl)	<200	178	211	182	235	183
HDL (mg/dl)		32	32	39	30	52
LDL (mg/dl)		68	114	102	123	104
IGF1 (ng/ml)		64	150	143	162	300
Insulin (micU/ml)	2.6-25	12.6	14.9	10	51	4.9
HbA1C (%)		6.78				4.8
HIV Ab		Negative	Not checked	Not checked	Not checked	Not checked
AGPAT2 mutation		Homozygote	Heterozygote	Heterozygote	Negative	Heterozygote

WBC: Wight blood cell; MCV: Mean cell volume; ALKP: Alkaline phosphatase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; IGF1: Insulin-like growth factor 1; HbA1C: Hemoglobin A1c; HIV Ab: HIV Antibody; AGPAT2: 1-acylglycerol-3-phosphate-O-acyltransferase 2.

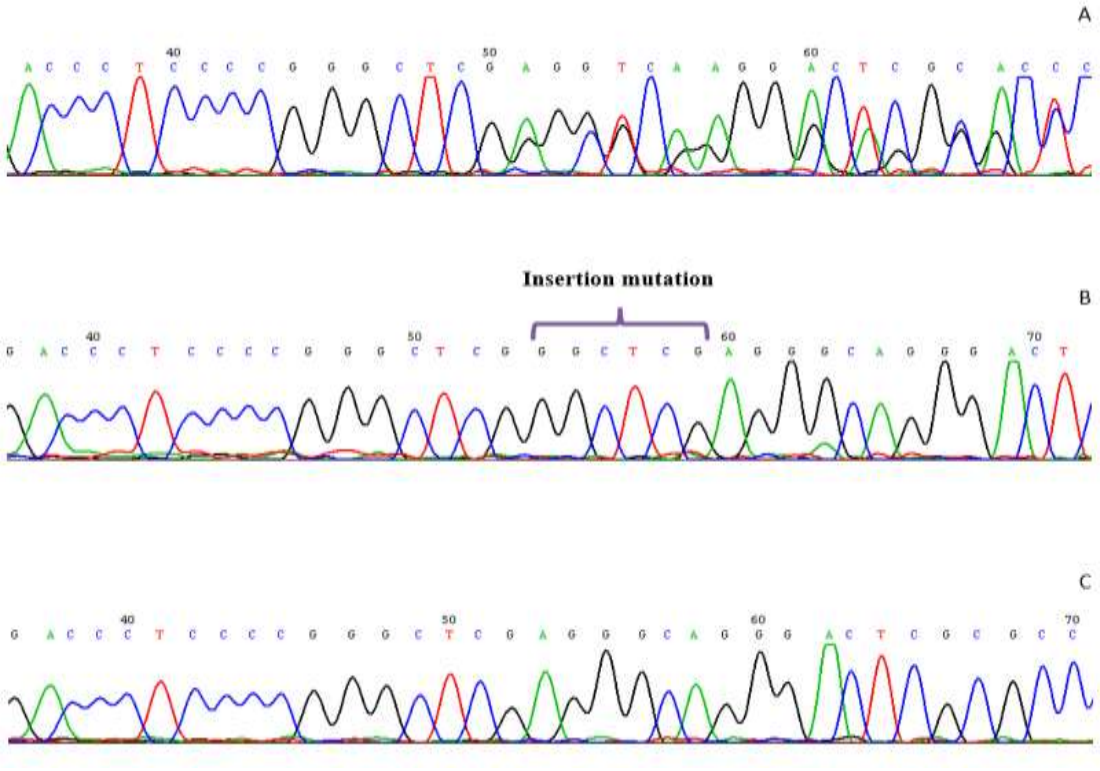

Fig.3: The chromatogram depict presence of indel mutation (rs145169122) in three member of family (A) heterozygote (B) homozygote (C) Normal.

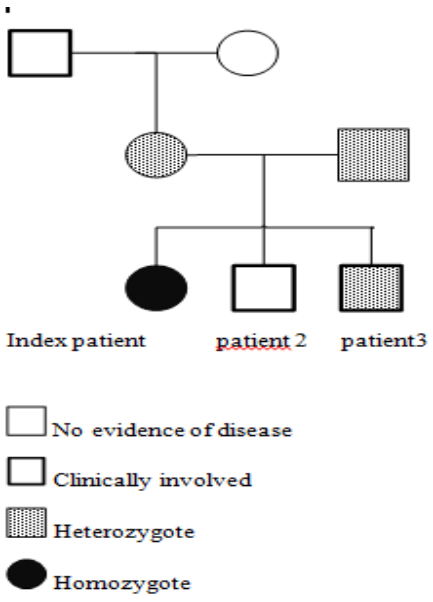

Fig.4: In this pedigree the grandfather had clinical appearance like the index case, he had died when he was about 50 years. The parents both were heterozygote without any clinical and Paraclinical feature. Her brothers had athletic appearance and one of them was heterozygote too.

3- DISCUSSION

Our Index patient was diagnosed as congenital generalized lipodystrophy in adulthood with sclerotic and lytic bone lesions and positive AGPAT2 mutation. The congenital form of generalized lipodystrophy (CGL) or Berardinelli-Seip syndrome is a rare autosomal recessive disorder with near complete loss of adipose tissue from birth or up to first year of life, leading to a muscular appearance and prominent veins. Although in some patients, as our case, it might be diagnosed later in adulthood (6, 14).

Leptin has an essential role in regulating the energy homeostasis, neuroendocrine function, metabolism and immune function besides glucose, lipid and bone metabolism (15). Hyperphagia is seen which may be due to leptin deficiency. CGL patients grow at an accelerated rate during childhood and have advanced bone age (16). Hands, feet and jawbone may enlarge and make an acromegaloid facial appearance as was detected in our case (8). Acanthosis nigricans as a manifestation of insulin resistance is evident. It is widespread and may involve trunk and chest. Glucose intolerance and diabetes mellitus appear during puberty. Hypertriglyceridemia is one of the major metabolic derangements that sometimes can be so severe that it may lead to pancreatitis or painful eruptive xanthoma (17). Hepatomegaly due to liver steatosis is common, and can develop to steatohepatitis and cirrhosis. Splenomegaly and umbilical hernia or prominent umbilicus are other clinical findings. Most of these clinical manifestations were positive in our case (Acromegaloid features, Acanthosis nigricans, Hypertriglyceridemia, Hepatomegaly and Splenomegaly).

In female patients, hirsutism, clitoromegaly, irregular menstrual periods, polycystic ovaries, and infertility may be present. However, male patients are reported to have normal reproductive function (4, 14). Primary amenorrhea was one of the symptoms of our patient. Bone manifestation of CGL includes sclerotic lesion before and lytic lesion after adolescence. Distinct sclerotic patches in early adulthood have been reported (12). Shynia et al. reported a 35-year-old CGL female patient with sclerotic lesion of the central skeleton (18). In the study of Fleckenstein et al. several focal lytic bone lesions and cyst formation in appendicular bone has been described (19). Lytic bone lesions in the appendicular bone are almost limited to the CGL adults with mutations in AGPAT2. Our case had both sclerotic and lytic lesions after puberty at the same time. Lytic lesions in long bones like the femur, tibia, and humerus in affected subjects with AGPAT2 mutation have been reported (12).

In the study of Van Maldegam on 70 affected individuals, the prevalence of bone cyst in CGL1 and CGL2 were 23.5% and 8.3%, respectively (10). Our case had lytic bone lesions in the femur and sclerotic bone lesions in the pelvic. There is no previous report for presence of this variant in patients with CGL. However, this neither confirms nor rules out pathogenic effect of this variant. Considering compatibility of candidate gene genotype, phenotype and chemotype, the pathogenicity of this variant might be considered. The diagnosis is built on clinical findings and can be confirmed by genetic studies. 1-acylglycerol-3-phosphate O-acyltransferase2 (AGPAT2) gene is located on chromosome 9q34 and is an essential enzyme for triglyceride and phospholipid synthesis. It catalyzes formation of phosphatidic acid from lysophosphatidic acid (3).

In mice, AGPAT2 mutation leads to loss of white and brown adipose tissue and subsequently hypertriglyceridemia, hyperinsulinemia, hyperglycemia and severe hypoleptinemia (SH). Even with AGPAT2 deficiency triglyceride synthesis was elevated in the liver. Based on

molecular analysis, the 54-fold increase of the expression of monoacylglycerol and a distinct lipogenic pathway by monoacylglycerol transferase1 may clarify the fat accumulation in liver and steatosis (20). Our patient was homozygous and her parents and her brother were heterozygous for that mutation (**Figure.2**). One of her brothers (patient 2) had athletic appearance, high levels of insulin and triglyceride, and mild to moderate fatty liver (grade 1-2) on US. However, he was negative for AGPAT2 mutation polymorphism. As he was overweight then some of these laboratory findings may be due to presence of metabolic syndrome. On the other hand, there is an accumulative gene in the family history, so it may be due to another undiagnosed mutation. The other brother (patient 3) had athletic appearance with acanthosis nigricans, but normal serum insulin level and no fatty liver on US. He was heterozygoous for AGPAT2 mutation.

The metabolic derangement and fat accumulation in the liver including non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) as well as cirrhosis, which threaten the patient's survival should be carefully treated. Diet modification and exercises were recommended to the index patient. Metformin 500 mg twice daily and pioglitazone 45 mg in a day were administered. Diabetes was controlled and insulin level was decreased to normal range after the treatment. However, after decreasing liver transaminases to the normal ranges, liver size and the markers of fatty liver did not change (**Tables.1 and 3**).

Hypertriglyceridemia can be controlled by fibrates and statins therapy. Our patient has been put on Gemfibrozil. In severe cases with very high triglyceride levels, plasmapheresis can resolve painful xanthoma and prevent pancreatitis (6). Leptin has a profound effect on regulating food intake, body weight, lipid and glucose metabolism, hypothalamic-pituitary axis, immunity, brain function and structure. In generalized lipodystrophy and in patients with partial lipodystrophy, in case of severe metabolic derangement or low leptin level, reducing Hemoglobin A1c (HbA1c) and triglyceride seems to be effective (21, 22). Patients with CGL have significant hypoleptinemia. Leptin markedly reduces insulin resistance (23). The first trial of leptin therapy by the National Institutes of Health (NIH) and Texas University on nine lipodystrophic patients (5CGL, 3AGL, 1FPLD) with severe hypoleptinemia, showed significant improvement in diabetes, hypertriglyceridemia and steatohepatitis. Three patients who were on 800–3000 units of insulin a day could discontinue insulin (5, 24).

Ebihara et al. and Chan et al. used leptin therapy in seven generalized lipodystrophy patients (2 acquired and 5 congenital). They mentioned similar benefits (25, 26) and also improvement in micro- and macroalbuminuria, glomerular filtration rate and acanthosis nigricans. Moreover, no deterioration of retinopathy and neuropathy was found. Leptin therapy was found effective and safe in long term therapy for lipodystrophy and its associated complications (26). Chan et al. reported similar improvement in metabolic derangement (25). Steatohepatitis is one of the most important complications of generalized lipodystrophy which contributes to morbidity and mortality. Leptin replacement therapy reduces intrahepatic fat accumulation and serum liver transaminases. These changes have been demonstrated by MRI and liver biopsy (27). Spontaneous menarche and conceive has been reported among young women with CGL after leptin therapy (28). With regard to cosmetic management of lipodystrophy, reconstructive surgery with free flap, transposition of facial muscle and silicone implant in the cheeks can be used. For treatment of acanthosis nigricans in

generalized lipodystrophy, Etretinate and fish oil may have beneficial effects in some patients with CGL (7).

4- CONCLUSION

Congenital generalized lipodystrophy is a rare disorder characterized by near total loss of adipose tissue from birth through the first year of life. Severe leptin deficiency and insulin resistance is reported to lead to several metabolic derangements including diabetes, hypertriglyceridemia, liver steatosis, hyperandrogenism, and impaired reproductive functions in females.

Leptin deficiency has an essential role in metabolic derangements and leptin replacement therapy significantly improves metabolic derangements, insulin resistance and steatohepatitis. Bone cyst is one of the manifestations of CGL with AGPAT2 mutation. Patients usually have sclerotic bone lesions before and lytic bone lesions after puberty. Our patient had lytic bone lesions in (femur) long bones and also sclerotic lesions in the pelvic which was related to AGPAT2 mutation.

5- CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

6- ACKNOWLEDGMENT

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