

## CASE REPORT

# Oil Red-O Positive lipid blobs on peripheral blood film examination in a muscular infant with the diagnosis of Berardinelli–Seip syndrome

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## Abstract

Lipodystrophy syndromes can be acquired or hereditary in nature and are characterized by abnormal fat distribution including the inability of the body to develop and sustain healthy adipose tissue. They may be generalized or partial in nature. The congenital generalized form is termed as Berardinelli–Seip syndrome and may occur due to mutations in the *AGPAT2* or *BSCL2* genes. In this case report, we present an infant diagnosed with type-1 Berardinelli–Seip syndrome due to pathogenic variation in the *AGPAT2* gene. Though this type of lipodystrophy is less severe than the type-2 form, the case highlights the early presentation of the condition in infancy with increased frequency of stools and hypertriglyceridemia. In addition, we want to highlight that identification of characteristic physical appearances and recognition of abnormal findings during basic investigations is important, which can guide a clinician in making a correct diagnosis.

## INTRODUCTION

Congenital generalized lipodystrophy is a disease of abnormal fat metabolism and manifests in early childhood with insulin resistance, low fat stores and muscular hypertrophy. The awareness about the characteristic phenotype and clinical profile in a child who has failure to thrive can help make an early diagnosis and can prevent long term complications. In addition, due importance to basic investigations like the presence of milky serum and lipid droplets on peripheral blood film (PBF) can help clinicians investigate for a dyslipidemic profile and arrive at a close differential diagnosis. Herein, we highlight a case of an infant who presented with loose stools at birth and was noted to have congenital lipodystrophy on meticulous clinical, biochemical and genetic assessment.

## CASE REPORT

A 2-month-old breastfed baby, presented with an increased frequency of stools since birth. He was born at term with a smooth perinatal transition. His birth weight was 2.5 kg and his family history was unremarkable. Examination showed weight of 4.6 kg (between 0 to –2 z score as per WHO growth charts), multiple areas of loss of fat pads with loose folds of skin, giving a muscular appearance to the infant (Fig. 1a). There was no clinical evidence of insulin resistance but hepatomegaly was noted. Blood samples sent for hemogram showed grossly milky white plasma and a PBF examination revealed extensive pale pinkish white blobs in background strongly Oil-Red-O stain positive confirming it to be lipoid in nature (Fig. 1b). Further biochemical analysis revealed extremely high triglyceride levels

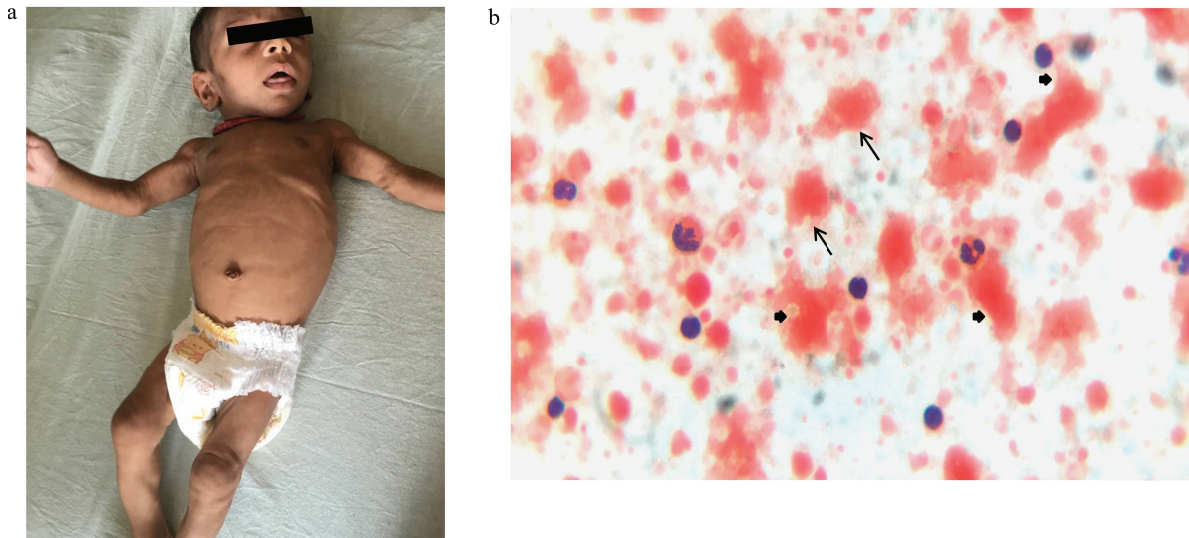
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**Figure 1:** (a) Muscular infant with loss of fat pad and prominent chin, (b) Oil-Red-O positive lipid blobs (black arrows) on peripheral blood smear examination.

(random 17 000 mg/dl, fasting 7224 mg/dl) and cholesterol (858 mg/dl). There was no evidence of pancreatitis due to normal amylase and lipase levels and a normal ultrasonography. Liver function tests were normal and liver ultrasonography showed no evidence of cirrhosis. Family screening was normal for lipid levels. A possibility of congenital lipodystrophy or type 1/type 5 familial hyperlipidemia was considered and clinical exome sequencing was advised. Next generation sequencing revealed a novel homozygous pathogenic INDEL in *AGPAT2* gene (c.667\_705delGTCACAGTGCAGGTGCTGGAAGCCATC CCCACCAGCGG CinsCTGCG) (p.Val223LeufsTer19), consistent with a diagnosis of congenital lipodystrophy type 1 or Berardinelli–Seip syndrome. The child was started on low fat medium chain triglycerides based powder formula and fat-soluble vitamin supplements and discharged in a hemodynamically stable state with advice for closer follow up with serial weight monitoring, developmental assessment and ultrasonography of abdomen to look for evidence of pancreatitis and early signs of liver cirrhosis. Cardiac angiographies are also planned in follow up to detect early coronary artery atherosclerotic abnormalities. In the last follow up of 6 months duration, the stool pattern has normalized, the baby has gained weight and continues to gain developmental milestones as per age. The triglycerides have come down to 1500 mg/dl. Since there has been a response to dietary modifications, we plan on continuing low fat diet lifelong along with vitamin supplements.

## DISCUSSION

Berardinelli–Seip syndrome is a rare autosomal recessive condition first described in 1954 by Berardinelli and later confirmed by Seip in 1959. It has a prevalence of 1 in 10 million and close to 250 patients have been described to date. It is characterized by the absence of functional adipocytes at birth. This leads to abnormal fat deposition in the liver and skeletal muscle giving rise to hepatomegaly and muscular or athletic appearance to the child [1–3]. The diagnosis is based on a clinical criterion that are a major and minor sub-criteria. The major criteria include presence of lipoatrophy affecting both trunk and limbs, acromegaloid habitus, hepatomegaly, hypertriglyceridemia and

evidence of insulin resistance. Minor criteria include presence of hypertrophic cardiomyopathy, psychomotor or mental retardation, hirsutism, precocious puberty in females and bony cysts in epiphyseal and metaphyseal regions of long bones [2]. The confirmation of the disease requires genetic analysis with presence of pathogenic variations in the *AGPAT2* or *BSCL2* gene. Usually, cases with *BSCL2* gene mutations are more common and have psychomotor retardation and more severe lipodystrophy. Patients with *AGPAT2* mutations have less than 10% incidence of associated intellectual disability and they have preserved fat in areas where it serves mechanical functions e.g. in palm, sole and periorbital areas. This was also seen in the index case [1]. *AGPAT2* gene produces an enzyme that is involved in the pathway of production of glycerophospholipids and triacylglycerols (which are major component of cell membranes and adipose tissue). Mutations in this gene are suggested to lead to reduction in triacylglycerol synthesis and storage in the fat cells. The mutations in this gene also cause high lysophosphatidic acid that impairs adipose tissue function [4]. Most of these cases tend to develop insulin resistance and metabolic syndrome phenotype in second decade of life. There is also a risk of recurrent pancreatitis and hepatic steatosis leading to liver cirrhosis due to persistent hypertriglyceridemia.

Congenital lipodystrophy may present in early infantile age and hence awareness of the clinical phenotype and characteristic physical appearance along with a high index of suspicion is a must for clinicians to diagnose and initiate preventive interventional measures. The case also highlights the importance of simple basic tests like noticing milky plasma or presence of lipid blobs on a PBF, that can alert a clinical and laboratory scientist to initiate further biochemical and mutational work up to make a correct diagnosis.

## CONFLICT OF INTERESTS

None.

## FUNDING

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### **ETHICAL APPROVAL**

Due ethical approval by departmental review board was taken.

### **CONSENT**

Written and informed patient consent was taken from both the parents for the image.

### **GUARANTOR**

Dr. Prateek Bhatia (corresponding author).

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None.

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