

Berardinelli-Seip congenital lipodystrophy

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Abstract

Berardinelli-Seip congenital lipodystrophy (BSCL) is a very rare autosomal recessive disorder determining the triad of lipoatrophy, hypertriglyceridemia, hepatomegaly and acromegaloïd features. It is associated with insulin resistance resulting in clinically overt diabetes mellitus with onset during the second decade. Complications include hypertrophic cardiomyopathy, a fatty liver with hepatic dysfunction, muscular hypertrophy and a number of endocrine disturbances (accelerated growth in infancy, precocious puberty, ...) and bone cysts with spontaneous fractures. There are at least three loci among which two are localized (BSCL1 in 9q34 and BSCL2 in 11q13) and one gene already cloned (seipin for BSCL2). Mental retardation is observed in a majority of BSCL2 patients. Treatment consists of low fat diet and handling of insulin resistance and diabetes.

Keywords

adipose tissue - diabetes mellitus - mental retardation - seipin - triglycerides -autosomal recessive inheritance.

Disease name and synonyms

It is called Berardinelli-Seip syndrome after Berardinelli from Brazil described the first patients in 1954. The syndrome was confirmed in 1959 in Norway where Seip described a new series of patients originating from the county of Rogaland. In the European literature, the terms generalized lipodystrophy, congenital lipodystrophy or total lipodystrophy have also been coined. Seip syndrome, or Lawrence

syndrome have also been used, although the latter designates in principle the so-called acquired form. It is usually called lipoatrophic diabetes in the United States. It has received the OMIM number [269700](#). Brunzell syndrome is the association of bone cysts and lipoatrophic diabetes described in five affected African-Americans from the same sibship. A separate OMIM entry ([272500](#)) was given but it is now generally admitted that bone cysts represent a

rare complication of Berardinelli-Seip congenital lipodystrophy (BSCL).

Excluded diseases

- Lawrence syndrome
- Dunnigan partial lipodystrophy
- Barraquer-Simons syndrome
- Partial congenital lipodystrophy with elevated C3 nephritic factor
- Rabson-Mendenhall syndrome
- Launois-Bensaude syndrome
- Wiedemann-Rautenstrauch
- SHORT syndrome
- AIDS lipodystrophy
- Russell diencephalic syndrome

Diagnostic criteria

Major

- Lipoatrophy affecting both trunk and limbs. Gives an athletic appearance, especially when muscle hypertrophy is also present. Secondary phlebomegaly. Involvement of the face (empty cheeks due to absence of Bichat's pads) may be absent at birth and appear during the first months of life.
- Acromegaloid features : it includes prognathism, salient orbital ridges, enlarged hands and feet, macrogenitosomia, gigantism, muscular hypertrophy and advanced bone age.
- Hepatomegaly secondary to fatty liver and, in late course of the disease, cirrhosis.
- Elevated serum concentration of triglycerides (up to 80g /Liter), sometimes associated to hypercholesterolemia.
- Insulin resistance : may be limited to elevated serum concentration of insulin and C-peptide in the first years of life. Will usually determine overt clinical diabetes during the second decade. Its early clinical expression is acanthosis nigricans of the groins, neck and axillae which may take, in some cases, a verruquous appearance.

Minor

- Hypertrophic cardiomyopathy. May be present in infancy or develop later in life.
- Psychomotor or mental retardation. Affects a majority of BSCL2 patients. Mild (IQ 50-70) to moderate (IQ 35-50)
- Hirsutism : low frontal and posterior hairlines, hypertrichosis of the trunk
- Precocious puberty in the female.
- Bone cysts. Polycyclic appearance on X-rays. Located in epiphyseal and metaphyseal regions of long bones. Often diagnosed during the second decade.

Differential diagnosis

In the infant

- Short syndrome. Slit lamp examination. Short stature.
- Neonatal progeroid syndrome. Prominent veins of the scalp. Premature teeth. Pseudo hydrocephaloid appearance.
- Neurometabolic lysosomal storage disorder: Gaucher type 2, Krabbe disease. Abnormal neurological examination. Glucocerebrosidase and galactocerebrosidase on peripheral leukocytes or cultured fibroblasts.
- Russell diencephalic syndrome. Brain MRI

In the child

- Dunningan lipodystrophy. Spares the face. Cushingoid appearance. Mutations in the lamin gene.
- Rabson-Mendenhall. Pure insulin-resistance syndrome
- Insulin-dependent diabetes mellitus

In the adult

- Barraquer-Simons syndrome. Asymmetric.
- AIDS. HIV testing
- Partial lipodystrophy. C3 nephritic factor
- Lawrence syndrome

Prevalence

Estimated at 1 per 12 millions by Garg in USA
 1 per million in Norway
 1 per 200 000 in Lebanon
 1 per 500 000 in Portugal
 according to the number of registered cases of the Berardinelli-Seip study group.

Clinical description

Neonatal or infantile presentation

Severe forms may be of prenatal onset with intrauterine growth retardation. When diagnosed at birth (rare), it is usually because of lipoatrophy. Reason for referral in the first months of life include failure to thrive, or conversely gigantism, hepatomegaly, lipoatrophy, facial dysmorphism, enlarged tongue or developmental delay.

Juvenile presentation

Accelerated growth, lipoatrophy or cognitive impairment are major modes of presentation in early childhood while diabetes mellitus manifested by weight loss, polydipsy, polyuria or asthenia is frequently the cause in the second decade.

Adult presentation

Presents rarely in early adulthood with diabetes mellitus. The plastic surgery clinic for cosmetic improvement of facial lipoatrophy, the cardiologic clinics or gastroenterologic clinics may be also the first through which the patient comes to medical attention.

Management

Diagnostic work-up

Family history, including a three generation pedigree and the locality of origin of the grandparents needs to be investigated. Specific questions on parental consanguinity should be asked for.

Clinical examination includes the pubertal status according to Tanner's charts, a complete neurological examination and search for signs of liver dysfunction and cardiac failure. Attention must also be paid to possible orthopedics problems (reduced hip mobility, genu valgum).

Additional investigations

- Clinical chemistry : Complete blood count, electrolytes, serum glucose concentration, insulin, aspartate transaminase, alanine transaminase, serum proteins and electrophoresis, urea, creatinine, C-peptide, triglycerides, cholesterol, Oral glucose tolerance test. When appropriate : clamp glucose homeostasis study, GH, IgG, A, M, E, C3 nephritic factor, CH50, C3, C4, apolipoproteins, hypothalamo-pituitary dynamic tests.
- Cardiac ultrasound
- Liver ultrasound
- Skeletal survey, especially long bones. Search for osteopenia and bone cysts. Bone age maturation
- Kidney ultrasound
- Complete ophthalmological examination, including biomicroscopy and slit lamp examination
- Wechsler testing of IQ
- DNA testing (search for a *BSCL2* mutation or 9q34 microsatellites segregation study). Collect also leukocytes from unaffected siblings and parents after informed consent (15 ml EDTA purple top tubes)

Handling

Restriction of total fat intake between 20 and 30% is often sufficient to maintain a normal triglycerides serum concentration. Hypercholesterolemia is rarely in the range requiring anticholesterol drugs. Medium chain triglycerides may provide an additional effect and should be used when low fat diet alone is

insufficient. The other drugs, including fenfluramine, have no proven efficiency and should be avoided.

The patient will have to be followed in a diabetology clinic for possible retinal, peripheral nerve and renal complications one outpatient consultation every six months.

Cardiac and liver ultrasound will have to be repeated every six months.

Special education will be required for most *BSCL2* patients

Etiology

Rare autosomal recessive disorder with at least three loci identified:

BSCL1:prevalent in Africa, Maghreb and African populations from North America and Caribbean. Also described in Western European populations. Apparently less severe phenotype than *BSCL2*. Onset of lipoatrophy may be the second or third decade. No or low frequency of mental retardation. Linkage to 9q34 established by an Anglo-American consortium in 1999.

No gene with disease-causing mutation identified up to now.

BSCL2:prevalent in Portugal and its ancient colonies, Lebanon and Norway. Lipoatrophy of invariable neonatal onset. More severe than *BSCL1*. A majority of patients (two-thirds) mentally retarded, especially those with a nonsense or a splice-site mutation affecting the first half of the gene. Missense mutations reportedly less harmful. In a recent survey of 45 *BSCL2* patients, 7 premature deaths were observed, from heart and liver failure. Through the study of patients from an international consortium, a gene has been cloned in 2001. It encodes a protein of unknown function, mainly expressed in the brain, termed seipin (Magré *et al* 2001)

BSCL3:some rare families appear unlinked to neither 11q13 nor 9q34. If we also consider a patient with inconclusive segregation study, it seems associated with a severe phenotype (two premature deaths at 16 months and 7 years in two Czech patients). However, these are very scarce data and awaits confirmation on additional families

Diagnostic methods

Dysmorphology

Clinical examination

Blood chemistry

Genetic counseling

Recurrence risk 25%

Microsatellites segregation study and mutation screening mandatory to refine counseling.

Prenatal diagnosis

Based on the identification of the mutation in the index patients or carriers.

Chorionic Villus Sampling between 9 and 12 weeks.

Ethical issue of terminating a pregnancy for the apparently milder *BSCL1* subtype where mental retardation is rare.

Unresolved questions

Function of the protein

Pathophysiology of the disease

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