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Case report

Berardinelli-Seip syndrome in peritoneal dialysis☆

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ABSTRACT

A case of Berardinelli-Seip syndrome, a congenital generalised lipodystrophy, is reported. Symptoms first appeared when the patient was 20 years old. She showed severe insulin resistance as well as micro- and macro-angiopathic complications, including chronic kidney disease, which required renal replacement therapy with peritoneal dialysis. The patient's clinical course was reviewed since paediatric age (when initial signs of the disease being already evident) to present time. Berardinelli-Seip syndrome is very uncommon, and the present case is particularly rare because it is the only case (at least as reported in the literature) in a patient receiving dialysis.

Síndrome de Berardinelli-Seip en diálisis peritoneal

Palabras clave:
Síndrome de Berardinelli-Seip
Enfermedad renal crónica
Nefropatía diabética
Diálisis peritoneal

RESUMEN

Se describe el caso de una paciente con síndrome de Berardinelli-Seip, un tipo de lipodistrofia congénita generalizada, que inició a los 20 años, con marcada resistencia insulínica y complicaciones micro- y macroangiopáticas, entre ellas una enfermedad renal crónica que la ha llevado a iniciar tratamiento renal sustitutivo en la modalidad de diálisis peritoneal. Para ello llevamos un repaso de la historia de la paciente desde la edad pediátrica (momento en el que ya aparecen los primeros signos de la enfermedad) hasta la actualidad. Más allá de lo infrecuente de esta enfermedad, es de destacar que lo excepcional del caso es que se trata del único caso (al menos registrado en la literatura) de pacientes afectos de síndrome de Berardinelli-Seip en programa de diálisis.

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Introduction

Berardinelli-Seip syndrome is an extremely rare disorder that belongs to other group of congenital generalised lipodystrophies. The lipodystrophies are a heterogeneous group of diseases, which can be congenital or acquired, characterised by a partial or total absence of adipose tissue, along with insulin resistance, hypertriglyceridemia, low HDL cholesterol, liver disease, and renal disease, with proteinuria usually in the nephrotic range, and increased cardiovascular risk. They can be classified into generalised/localised and congenital/acquired. The most prevalent form is acquired (localised or generalised), secondary to anti-HIV antiretroviral therapy.

Berardinelli-Seip syndrome was first described in 1954 by Berardinelli[1] in 2 children, and in 1959 by Seip[2] in 3 more patients. It has an autosomal recessive transmission and a prevalence of 1/10 000 000.[3] The syndrome can be caused by 3 characteristic mutations: type 1 is caused by a mutation in the *AGPAT2* gene (on exon 9q34), which codes for the enzyme 1-acylglycerol-3-phosphate O-acyltransferase 2; type 2 is caused by a mutation in the *BSCL2* gene (on exon 11q13), which codes for the protein seipin (and is generally associated with a worse prognosis); and type 3 is due to a mutation resulting in altered synthesis of the membrane protein CAV_1. Ninety-five percent of patients have one of the first two mutations.

The disease is characterised by an almost complete absence of adipose tissue, from birth, affecting practically the entire body. It is associated with insulin resistance (it can lead to the development of diabetes), dyslipidaemia (due to hypertriglyceridemia and low HDL), hepatic steatosis, muscular pseudohypertrophy (Fig. 1), acromegalic features (Fig. 2) and accelerated growth, acanthosis nigricans, and reduced concentrations of leptin and adiponectin. All these conditions accelerate the process of atherosclerosis and the development of cardiovascular disease with microangiopathic and macroangiopathic complications. Furthermore, up to 25% of patients have hypertrophic cardiomyopathy.[4,5]

Occasionally, patients develop chronic kidney disease (CKD). This is probably related to the presence of diabetic nephropathy, although (as with other lipodystrophies) an association has also been described with focal sclerosing glomerulopathy and with membranoproliferative glomerulonephritis.[6–9]

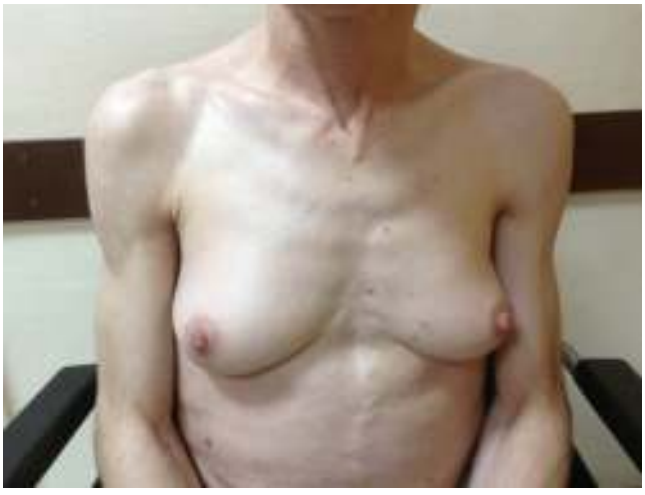

Fig. 1 – Thoracic muscular pseudohypertrophy.

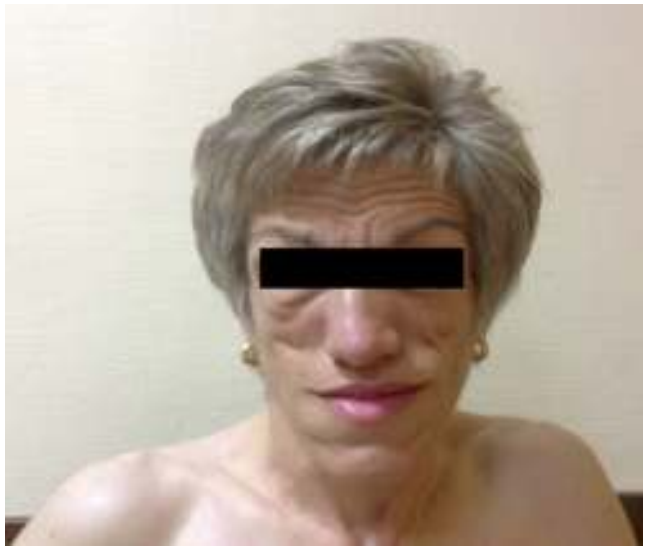

Fig. 2 – Acromegalic features.

Due to its low prevalence, there is scarce information of Berardinelli-Seip syndrome in the literature. To the best of our knowledge, there have been few cases that developed CKD, and no described cases of patients on peritoneal dialysis. It should be noted that whilst the definitive diagnosis of this disease is with the detection of a mutation, the complete lack of adipose tissue along with muscular hypertrophy in the absence of other criteria is also sufficient for the diagnosis.

Clinical case

We present the case of a patient born in 1961, with no history of consanguinity or lipodystrophy. At 6 years old, she underwent umbilical hernia repair, at which time she was noted to have hepatomegaly of 2 cm (with no further investigation at that time). At 11 years old, she was diagnosed with asymptomatic multinodular goitre, and serial follow-up ultrasound studies were performed. In 2002, she underwent surgery for airway compression and has had hormone replacement therapy since then. At 20 years old, she had a non-functioning pituitary adenoma; an acromegaly screen was performed (due to the patient's then acromegalic features): somatomedins and growth hormone stimulation test were normal.

The cardinal clinical symptoms of diabetes mellitus began at puberty; raised peptide C and marked insulin resistance confirmed this. From the time of diagnosis, her diabetes did not respond well to treatment, remaining poorly controlled despite high doses of insulin (up to 5 IU/kg) and several oral antidiabetics. Glycosylated haemoglobin (HbA1c) has always been poorly controlled, reaching up to 13%. She has significant macroangiopathic and microangiopathic complications, with chronic lower limb ischaemia (Fontaine stage III–IV) that has led to multiple phalangeal amputations in both feet (2003, 2004, 2007, and 2014). She also has grade I–II retinopathy and

marked peripheral neuropathy (diagnosed in 2000), which over time has become disabling, and since 2008 she has been mobilising using a wheelchair. In addition, over the years, it became evident that she had detrusor hypotonia (attributed to diabetic neuropathy), leading to megabladder, grade I vesicoureteric reflux, and recurrent urinary tract infections.

At age 38 years, she was noted to have abnormal liver function tests; therefore in 2002, she underwent a liver biopsy. A diagnosis was made of Child–Pugh stage A cirrhosis secondary to hepatic steatosis, with portal hypertension and development of oesophageal varices without bleeding episodes. Treatment with propranolol was started. She had one episode of hydropic decompensation in 2008 that resolved with conservative treatment.

Another associated problem was the onset of leukopenia and thrombocytopenia that became persistent. She was assessed by the haematology team who performed a bone marrow biopsy in 2002, which was reported as normal; the bicytopenia was attributed to hypersplenism secondary to portal hypertension.

It was in 2005 that the possibility of Berardinelli-Seip syndrome was raised (in view of the multiple diseases she had presented with over the years). Therefore, a genetic study was performed. Unfortunately, for technical reasons, it was not possible to sequence exon 4 of the *BSCL2* gene. In the other 11 exons, there were no mutations. The conclusions of the geneticists was that she must have a deletion of this exon. Despite no mutation being found, the diagnosis of Berardinelli-Seip syndrome was established, based on the publication by Garg,[4] which stated that even if a mutation in the genes described above is not detected, patients who meet the essential criteria of a generalised lack of body fat and hypermuscularity from birth can be given this diagnosis.

This patient was referred to our endocrinology outpatient department in 2008 for nephrotic proteinuria (of up to 6 g/24 h), with normal renal function, and normal immunology (except for a mildly elevated IgA). Urinalysis and urinary sediment were unremarkable, and abdominal ultrasound showed kidneys of normal size with pelvicalyceal dilatation. At that time, renal biopsy was not performed and the clinical signs were attributed to diabetic nephropathy. It was decided then to block the renin–angiotensin–aldosterone system with an ARB, and no further investigations were performed at that time. Renal function remained stable until June 2012, when, with no particular trigger, serum creatinine rose to 2.8 mg/dL, and creatinine clearance fell to 9 mL/min, with a proteinuria of 4 g/24 h. Serum and urine immunofixation detected an IgG kappa and an IgG lambda component, which was attributed to a polyclonal gammopathy of undetermined significance. It was then that the diagnostic doubt arose between probable diabetic nephropathy, membranoproliferative glomerulonephritis (associated with Berardinelli-Seip syndrome, but seemingly unlikely given the unremarkable sediment), focal segmental glomerulonephritis associated with vesicoureteric reflux, and hepatorenal syndrome associated with cirrhosis. At that time, the possibility of performing a renal biopsy was assessed, but ruled out due to the marked thrombocytopenia and the fact that it was unlikely to change her management; the condition was managed conservatively. A recent transthoracic echocardiogram showed hypertrophic cardiomyopathy with signs suggestive of fatty infiltration, compatible with the expected findings in this disease.

The patient was admitted again in 2013 due to worsening renal function with no obvious cause, but with marked uraemic symptoms in the form of nausea and vomiting that lead to her starting renal replacement therapy. A peritoneal high flow swan-neck catheter (Fresenius Medical Care®) was surgically placed by the general surgery team without complications. After a month, she started continuous ambulatory peritoneal dialysis with biocompatible solutions, which she tolerated and adapted to well.

The dialysis schedule included three exchanges daily, one with a low glucose concentration, another with icodextrin, and the third with amino acids to minimise the risk of malnutrition. Since then she has had acceptable Kt/V and adequate volume management, maintaining a residual diuresis of around 1500 mL/day. Since starting this technique, the only incidents have been one episode of peritoneal infection due to *staphylococcus epidermidis*, which resolved with specific AB treatment, and amputation of the first right toe due to ischaemia/necrosis.

Conclusions

We presented this case because it seemed important for several reasons, including the low prevalence of the disease itself and the lack of published cases of Berardinelli-Seip syndrome during renal replacement therapy. This case was an example of how, even in patients with a poor survival prognosis, appropriate management of CKD (first in outpatients and then in our unit for advanced CKD) and the option of non-aggressive techniques can offer patients a good quality of life (based on quality of life questionnaires such as Euroquol and SF-36).

No specific treatment for Berardinelli-Seip syndrome was given; we aimed to control the different problems arising over the course of the disease. This involved using lipid-lowering therapy, dietary measures, cosmetic surgery, and, of course, dialysis.

The usefulness of treatment with leptins (r-met-Huleptin) in patients with lipodystrophy has been described, achieving a reduction in HbA1c, hypertriglyceridaemia, and hepatic volume, and normalising the caloric profile, as well as increasing satiety (all in the space of 4 months). However, there are no randomised studies that reliably demonstrate its usefulness.[10,11] Nonetheless, in our patient, given the marked abnormality in carbohydrate metabolism, the endocrinology team in our hospital completed the necessary application procedures to the National Institute of Health (NIH) to begin treatment with leptin. However, the supply of this drug was denied, because at that time, the use of recombinant leptin was not indicated in Berardinelli-Seip syndrome.

Conflicts of interest

The authors declare no conflicts of interest.

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