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Spondyloenchondrodysplasia with immune dysregulation related to *ACP5*. A report of 4 cases

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ABSTRACT

Spondyloenchondrodysplasia with immune dysregulation related to *ACP5* (SPENCDI, OMIM number 607944) is an uncommon immune-skeletal dysplasia with heterogeneous manifestations and variable severity. It is characterized by spondylar and metaphyseal lesions, immune dysfunction, and neurological involvement.

Here we report the clinical, radiological and genetic aspects of 4 girls with SPENCDI treated at a children's hospital. They all had skeletal manifestations and 3 developed severe immune disease. In 3 patients, the likely pathogenic variant c.791T>A; p.Met264Lys (homozygous mutation) was observed, while 1 patient had variants c.791T>A; p.Met264Lys and c.632T>C; p.Ile211Thr (variant of uncertain significance with pathogenic prediction based on bioinformatics algorithms) caused by a compound heterozygous mutation in *ACP5*. The repeated presence of variant c.791T>A suggests the possibility of a common ancestor in our population.

The recognition and diagnosis of this disorder is important to achieve a timely approach, which should be multidisciplinary and aimed at preventing possible complications.

Keywords: *spondyloenchondrodysplasia; autoimmune diseases; skeletal dysplasia; pediatrics;* ACP5 *gene.*

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INTRODUCTION

Spondyloenchondrodysplasia with immune dysregulation related to *ACP5* (SPENCDI #607944) (group 12 according to the Nosology and Classification of Genetic Skeletal Disorders)[1] is an autosomal recessive immune-skeletal dysplasia with a prevalence < 1/1 000 000 caused by mutations in the *ACP5* gene that encodes the tartrate-resistant acid phosphatase (TRAP) protein. Loss of TRAP function is related to an overproduction of interferon-alpha with predisposition to autoimmune diseases and decreased osteopontin dephosphorylation, which activates osteoclasts and promotes bone resorption.[2–5]

SPENCDI was first described as a condition by Roifman in 2000; it is radiologically characterized by dorsally accentuated platyspondyly, radiolucent and irregular lesions in the spine and in long bone metaphyses, that represent islands of chondroid tissue within the bone.[6]

Clinical signs and symptoms are heterogeneous, with a wide intra- and interfamilial variability. Growth retardation or short stature, kyphoscoliosis or limb misalignment secondary to skeletal involvement, neurological involvement characterized by brain calcifications with spasticity, motor clumsiness, intellectual disability, and manifestations secondary to immune dysregulation, such as autoimmunity and immunodeficiency, have been described.[3–5,7–9]

Here we report the clinical, radiological, and genetic aspects of 4 unrelated girls with SPENCDI who, due to suspicion or diagnosis of skeletal dysplasia, were referred to the Department of Growth and Development of Hospital Pediátrico H. J. Notti, in Mendoza, Argentina. The informed consent was obtained. The study was approved by the hospital's Ethics and Research Committee (minutes 39/2022).

CASE REPORTS

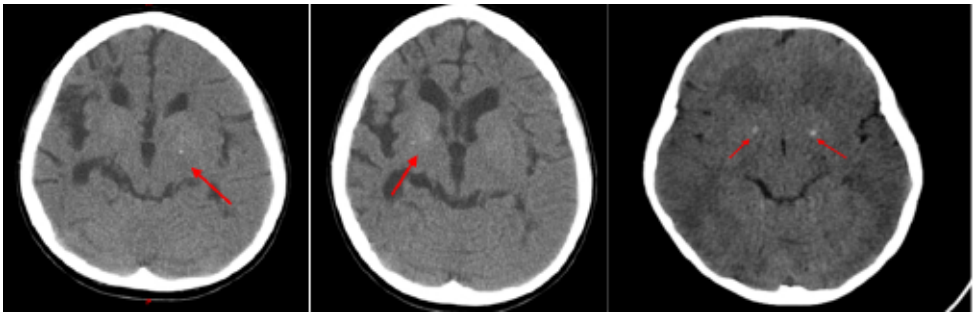
Patient 1. She was referred by the Department of Traumatology at 3 years old due to *genu valgum* and normal height. Her X-rays showed metaphyseal and vertebral dysplasia. Her humoral and cellular immune evaluation and chest and brain CT scans were normal.

She is not receiving any treatment at the time.

Patient 2. She was referred by the Department of Immunology at 9 years old for screening skeletal dysplasia associated with immunodeficiency. She had a normal height, intellectual disability with brain calcifications (*Figure 1*), and a sequela of hemiparesis. She also had associated immunodeficiency with recurrent febrile syndrome, septic shock, recurrent pneumonia, and ischemic stroke in the context of antiphospholypid syndrome. In addition, she had been diagnosed with autoimmune hypothyroidism at 4 years old, thrombocytopenic purpura at 6 years old, and autoimmune hepatitis at 10 years old.

She is currently being treated with intravenous gamma globulin, an immunomodulator (ruxolitinib) due to a refractory response to first-line immunosuppressants, and hydroxychloroquine with acetylsalicylic acid for the antiphospholypid syndrome. She had a partial response due to an intra-treatment relapse of cytopenia.

Figure 1. Computed tomography of patients with spondyloenchondrodysplasia and brain calcifications



A B C

A. Patient 2 (11 years old). Bilateral sequelae of atrophy with intracranial thalamic calcifications and caudate nucleus (B). C. Patient 4 (8 years old). Bilateral intracranial thalamic calcifications.

Patient 3. She was referred by the Department of Immunology at 2 years old for the screening of skeletal dysplasia associated with immunodeficiency. She had a normal height, generalized arthralgia, and splenomegaly. During the course of her disease, she developed cytopenia, fever, and lymphoproliferation and she was diagnosed with systemic lupus erythematosus (SLE) at 2 years old. She had a history of a sister who died at 20 months old due to refractory hemolytic anemia.

She is currently receiving ruxolitinib for her SLE with interstitial lung involvement together with mycophenolate mofetil and hydroxychloroquine, with an adequate response.

Patient 4. She was referred by her pediatrician at 6 years old due to short stature and growth retardation since 4 years old. She had short stature, intellectual disability, and brain calcifications (*Figure 1*). Her condition was associated with humoral immunodeficiency, hypocomplementemia, renal tubular acidosis, autoimmune hepatitis, and bronchiectasis. She had a history of septic arthritis in the right hip with bacteremia due to *Streptococcus pneumoniae* at 6 years old.

She is currently receiving treatment with azathioprine, a first-line immunosuppressant for autoimmune hepatitis and gamma globulin, with an adequate response.

All the patients were followed-up by a multidisciplinary team. Patients 2 and 4 received antibiotic prophylaxis due to lung involvement and alteration of humoral immunity.

Patients 1 and 3 underwent direct sequencing (Sanger) of the *ACP5* gene based on clinical and radiological data in both patients and also on the family history in patient 3. Patients 2 and 4 underwent exome sequencing using the Next Generation Sequencing (NGS) method for immune dysregulation and autoinflammatory conditions, respectively. In patients 1, 2, and 3, the *ACP5* gene had a likely pathogenic variant c.791T>A; p.Met264Lys caused by a homozygous mutation; in patient 4, variants c.791T>A; p.Met264Lys and c.632T>C; p.Ile211Thr were caused by a compound heterozygous mutation. The latter is classified as a variant of uncertain significance as per the criteria of the American College of Medical Genetics (ACMG)[10] at the time of the test, although it has a very low population frequency and pathogenic prediction as per the bioinformatics algorithms. Family segregation tests were performed in cases 1 and 3, and the same heterozygous variant was detected in the parents. None of the families mentioned a history of consanguinity.

Demographic, clinical, anthropometric, genetic/molecular, and radiological data are described in *Table 1* and *Figure 2*.

DISCUSSION

SPENCDI is a rare condition with heterogeneous clinical and radiological characteristics, combining bone, immune, and neurological manifestations, as was the case of our patients.[4,5,7–9,11] The presence of early-onset immune dysregulation, whether or not associated with short stature, with or without growth retardation or metaphyseal alterations, should be considered a highly suspicious sign for SPENCDI.[4,5,8,11]

In the cases reported here, the age at the time of onset was younger than 6 years, while in the bibliography, it has been mentioned to be from birth to 15 years old; and the time until diagnosis was, on average, 2 years, which evidences the difficulties in the diagnosis of such a rare disease.[4,7,8] Familial aggregation was first described by Schorr.[12] Only 1 of our patients had a family history of autoimmune disease, which accelerated suspicion and diagnostic confirmation at an early age. The pleiotropy of this condition and the high intra-familial variability make it necessary to actively search for it among siblings.[4] Although in our series no history of consanguinity was observed, the presence of the repeated variant c.791T>A suggests the possibility of a common ancestor.

The baseline manifestations in 3 of our patients were of autoimmune origin, as reported in other studies; being autoimmune thrombocytopenia and SLE the most common, as in 2 of our patients.[4,8,11] When the presentation of SLE is atypical, in children under 5 years of age and with a family history, SPENCDI should be suspected.[11,13,14] Most patients present with 3 or more immune defects during childhood, as in those reported in our series, so it is necessary to assess immunity before administering any immunosuppressive treatment and, in case of normal results, to conduct a close follow-up, given the variability in the age of onset.[4,5,11]

Height may be variable, ranging from normal to severe growth retardation with short stature, which worsens over the years.[4,9] It was reported as the second cause of consultation and may present as a sole manifestation.[4] The only patient

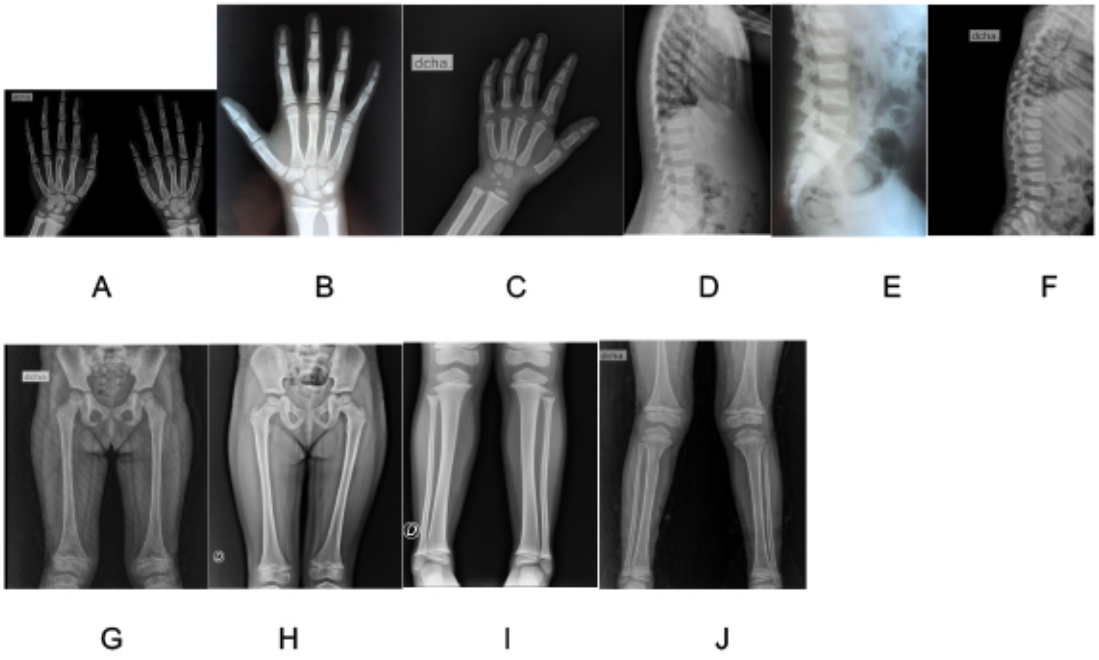
Table 1. Demographic, clinical, anthropometric, radiological, and genetic/molecular data of 4 patients with spondyloenchondrodysplasia

Patient	1	2	3	4
Current age (years)	6	11	3	8
Age at onset (years)	3	6	2	6
Age at diagnosis (years)	6	9	2	8
Family history	No	No	Sister who died at 20 months old due to autoimmune hemolytic anemia	No
Clinical manifestations	*Genu valgum*	**Baseline** -Septic shock -Stroke due to antiphospholypid syndrome -Autoimmune thrombocytopenic purpura **Current** -Humoral immunodeficiency -Autoimmune cytopenias -Recurrent fever -Recurrent pneumonia -Autoimmune hypothyroidism -Autoimmune hepatitis -Bronchiectasis	**Baseline** -Polyarthralgias -Splenomegaly **Current** -Systemic lupus erythematosus with joint, lung, and hematological involvement -Lymphoproliferation	**Baseline** -Septic arthritis -Bacteremia due to *Streptococcus pneumoniae* **Current** -Humoral immunodeficiency -Hypocomplementemia -Renal tubular acidosis -Autoimmune hepatitis -Bronchiectasis
Spasticity	No	Yes	No	No
Intellectual disability	No	Yes	No	Yes
Height (Z-score)	-0.8	-1.7	-0.7	-2.6
Metaphyseal dysplasia	++++	+++	++	+
Vertebral dysplasia (platyspondylia/nodular lesions/abnormalities in vertebral endplates)	++++	+++	++	+
Intracranial calcification	No	Yes	No	Yes
Genetic variant	p.Met264Lys (homozygous)	p.Met264Lys (homozygous)	p.Met264Lys (homozygous)	p.Met264Lys p.Ile211Thr (compound heterozygous)
Current immune treatment	No	-Antibiotic prophylaxis -Gamma globulin -Hydroxychloroquine -Ruxolitinib	-Mycophenolate mofetil -Hydroxychloroquine -Ruxolitinib	-Antibiotic prophylaxis -Gamma globulin -Azathioprine

in our series with short stature had other factors that could have impacted on her growth, such as severe infections and renal tubular acidosis, making it difficult to establish the primary cause of short stature.[5] Another reason for consultation is lower limb misalignment, present in 1 of our patients.[4]

Skeletal findings are an important diagnostic clue because they have to be present for diagnosis. There are different degrees of involvement, as in the cases described here, and the severity of skeletal manifestations may not be consistent with that of the other components, as evidenced in patient 1.[4]

Figure 2. Radiological characteristics of patients with spondyloenchondrodysplasia



A. Patient 1 (6 years old) and B. Patient 2 (9 years old). Metaphyseal changes and enchondromatoses of distal radius and ulna.

C. Patient 3 (2 years old). Metaphyseal abnormality of distal radius and ulna.

D. Patient 1 (6 years old) and E. Patient 2 (9 years old). Platyspondylia with abnormal vertebral endplate and lacunar lesions, located in the posterior third of the vertebral bodies.

F. Patient 3 (2 years old). Platyspondylia.

G. Patient 4 (8 years old) and H. Patient 1 (6 years old). Metaphyseal changes of the acetabular roof, proximal and distal femur. Shortening of femoral necks. Coxa vara.

I. Patient 1 (6 years old). Metaphyseal changes of distal femur, proximal and distal tibia, and fibula. Enchondromatosis of proximal fibula.

J. Patient 4 (8 years old). Mild abnormality of proximal and distal femur and distal tibia and fibula.

Among neurological manifestations, spasticity and intellectual disability are the most common ones.[4] Brain calcifications are described in more than 50% of patients. They are located in the basal ganglia, pons, dentate nucleus of the cerebellum, and at the level of the junction of the white and gray matter.[4] One of our patients had spasticity and 2 of them had intellectual disability and brain calcifications. We did not observe other features described, such as ataxia, seizures, psychosis, and painful multifocal neuropathy.[4]

Homozygous or compound heterozygous mutations have been reported in the *ACP5* gene with no obvious genotype-phenotype relationship.[4] The recurrent c.791T>A; p.Met264Lys mutation found in our patients has been previously described in association with this condition, and is classified as probably pathogenic according to the ACMG criteria.[3,4,7,10,15] In 1 of our patients, we found the variants c.791T>A; p.Met264Lys and c.632 T>C; p.Ile211Thr as compound heterozygous mutations; the latter is classified as a variant of uncertain significance (ACMG criteria); however, its low population frequency, the consistency with the clinical picture, and the predictions of pathogenicity as per several bioinformatic predictors may lead us to think about their involvement in the determination of SPENCDI in compound heterozygosis with the p.Met264Lys variant.

To date, the association between renal tubular acidosis and SPENCDI observed in patient 4 has not been described.

CONCLUSION

In this series of cases, we found heterogeneous clinical and radiological characteristics, as reported in the bibliography;

all patients had skeletal manifestations and 3 of them had severe immune disease.

The number of cases diagnosed with SPENCDI, a low prevalence disease, in a short period of time and the high frequency of the p.Met264Lys allele call for a future studies to delve deeper into the genetic characteristics of our population.

The clinical recognition of this condition is important for the diagnosis, treatment and multidisciplinary follow-up, as well as for the conduction of molecular studies. ■

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