

Spondyloenchondrodysplasia Due to Mutation in ACP5 Gene Presenting with Nephrotic Syndrome: A Case Report

Spondyloenchondrodysplasie aufgrund einer Mutation im ACP5-Gen mit nephrotischem Syndrom: Ein Fallbericht

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Key words

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Schlüsselwörter

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ABSTRACT

Spondyloenchondrodysplasia (SPENCD) with immune dysregulation (SPENCDI) is a rare autosomal recessive inherited immuno-osseous dysplasia characterized by spondylo-metaphyseal enchondromas, along with immune dysregulation ranging from immunodeficiency to autoimmune disorder. Here, we

present two cousins with ACP5 gene mutation who had severe short stature with mild hypogammaglobulinemia, nephrotic syndrome, autoimmune thyroiditis and cerebral calcification (Case 1); and in the other (Case 2), there was no clinical findings other than severe short stature, CD4+ T cell lymphopenia and non-autoimmune compensated hypothyroidism. We wanted to emphasize that monogenic causes should be considered in the etiology of early-onset nephrotic syndrome due to the detection of a mutation in the ACP5 gene (her actual diagnosis was changed to SPENCDI.) 5 years after the diagnosis of nephrotic syndrome in the first case, and that the renal involvement may occur without SLE in patients with ACP5 mutation. Severe short stature was a common finding in both cases. We underlined that the clinic can be different even in the same mutation, due to the absence of cerebral calcification and renal involvement in the second case, which is a cousin with Case 1. As a result, endocrinologists, immunologists, rheumatologists, nephrologists and orthopedists should be aware of this syndrome, because SPENCDI causes a pleiotropic (due to more than one phenotypic effect of a gene) clinical picture. Severe short stature may be the only presenting sign of patients with SPENCDI. In addition, in the presence of early-onset nephrotic syndrome and autoimmune thyroiditis, the patient should be evaluated for this type of monogenic disorders as well.

ZUSAMMENFASSUNG

Die Spondyloenchondrodysplasie (SPENCD) mit Immundysregulation (SPENCDI) ist eine seltene, autosomal-rezessiv vererbte immunossäre Dysplasie, die durch spondylo-metaphysäre Enchondrome und eine Immundysregulation gezeichnet ist. Letztere kann von Immunschwäche bis hin zu einer Autoimmunerkrankung reichen. Vorgestellt wird der Fall zweier Cousins mit ACP5-Genmutation. Einer von ihnen (Fall 1) wies einen schweren Kleinwuchs mit leichter Hypogammaglobulinämie, nephrotischem Syndrom, autoimmuner Thyreoiditis und zerebraler Verkalkung auf, während bei dem anderen Patienten (Fall 2) keine weiteren klinischen Befunde außer schwerem Kleinwuchs, CD4-positiver T-Zell-Lymphopenie und nicht autoimmunkompensierter Hypothyreose vorlagen. Bei der Ätiologie des früh einsetzenden nephrotischen Syndroms sollten monogene Ursachen in Betracht ge-

zogen werden, wie sich in Fall 1 zeigt. Hier wurde fünf Jahre nach der Diagnose des nephrotischen Syndroms eine Mutation im *ACP5*-Gen nachgewiesen, was zur Diagnose SPENCDI führte. Ebenso ist zu berücksichtigen, dass bei Patienten mit *ACP5*-Mutation auch ohne SLE eine Nierenbeteiligung auftreten kann. Schwerer Kleinwuchs war in beiden Fällen ein häufiger Befund. Zu beachten ist ferner, dass die Klinik auch bei derselben Mutation unterschiedlich sein kann, wie am vorliegenden Beispiel ersichtlich wird. Im zweiten Fall, der mit Fall 1 verwandt ist, lag keine zerebrale Verkalkung und keine Nierenbeteiligung vor.

Endokrinologen, Immunologen, Rheumatologen, Nephrologen und Orthopäden sollten sich dieses Syndroms bewusst sein, da SPENCDI ein pleiotropes klinisches Bild hervorruft (verursacht durch mehr als eine phänotypische Wirkung eines Gens). Schwere Kleinwüchsigkeit kann das einzige Symptom von Patienten mit SPENCDI sein. Darüber hinaus sollte der Patient bei Vorliegen eines früh einsetzenden nephrotischen Syndroms und einer Autoimmunthyreoiditis auch auf diese Art von monogenen Erkrankungen untersucht werden.

Introduction

Spondyloenchondrodysplasia (SPENCD) with immune dysregulation (SPENCDI) (OMIM 607944) is a rare autosomal recessive inherited immuno-osseous dysplasia characterized by spondylo-metaphyseal enchondromas, along with immune dysregulation ranging from immunodeficiency to autoimmune disorder [1, 2]. Neurological findings such as mental retardation, spasticity and cerebral calcification may also accompany the disease [3–5]. Short stature, rhizomelic micromelia, increase in lumbar lordosis, barrel-shaped rib cage, facial anomalies and difficulty in movement are seen due to bone anomalies. The clinic may differ even among members of the same family [3, 4]. In addition, autoimmune diseases (such as autoimmune thrombocytopenic purpura, hemolytic anemia, thyroiditis, systemic lupus erythematosus) are common manifestations of immune dysregulation [1, 3].

Here, we present two cousins with *ACP5* gene mutation who had severe short stature with mild hypogammaglobulinemia, nephrotic syndrome, autoimmune thyroiditis and cerebral calcification (Case 1); and in the other (Case 2), there was no clinical findings other than severe short stature, CD4+ T cell lymphopenia and non-autoimmune compensated hypothyroidism.

Case presentations

Case 1

A 10.5-year-old female patient was presented to the pediatric endocrine outpatient clinic with the complaint of short stature. From her history, it was learned that she was born 3200 g and 50 cm at term, was diagnosed with hypothyroidism at the age of 13 months and L-thyroxine treatment was started (ongoing). It was learned that at the age of 3.5, she was diagnosed with nephrotic syndrome due to membranous nephropathy and received dexamethasone (prednisolone) treatment for 2 years. In the kidney biopsy performed at that time, diffuse peripheral granular + 3, IgG, immune complex deposition was detected in the basement membranes of the glomeruli in the immunologic staining. Hematoxylin-eosin staining image is presented in ► Fig. 1. Antinuclear antibodies (ANA) and Anti-double stranded DNA (anti-dsDNA) were negative, C3 and C4 were normal. It was also learned that a 6.5-year-old was being followed up in the hematology division due to non-autoimmune ane-

mia and intermittent leukopenia. In the patient's family history, it was learned that there was a 5th degree consanguinity between the parents and that he had a healthy sister.

On physical examination, weight 25 kg (SDS - 1.7), height 120.4 cm (SDS - 3.1), fathom length 114 cm (SDS < - 3), sitting height 63 cm (SDS - 3), sitting height/height ratio 0.523 (SDS - 1.1), and growth rate 3.7 cm/year (SDS - 2.3). Thyroid was nonpalpable, puberty stage was compatible with breast Tanner stage 1. Her intelligence was normal, had no neurological anomaly, and other systemic examinations were normal. Other laboratory findings of the patient whose serum electrolytes were normal are given in ► Tables 1 and ► 2. Direct radiography showed platyspondyly, increased lumbar lordosis (► Fig. 2a), and irregularity in metaphyses (► Fig. 2b, c). And calcification in bilateral lentiform nuclei was seen in brain computed tomography (► Fig. 3). In the sent genetic analysis of the patient, a previously identified c.155 A>C (p.K52T) homozygous variant in the *ACP5* gene was detected. The same variant was found to be heterozygous in both parents. She is followed without medication, as she has mild proteinuria at the last control.

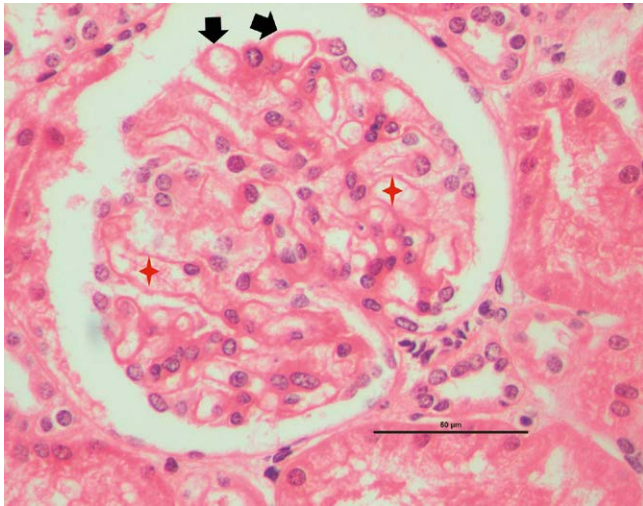
Case 2

A 12.5-year-old female patient (cousin of Case 1) was admitted to the pediatric endocrine outpatient clinic with the complaint of short stature. From her history, it was learned that she was born 3500 g and 49 cm at term. In her family history, it was also learned that there was no known consanguinity between the parents (from the same village), and that she had a healthy sister and a brother.

On physical examination, weight 31 kg (SDS - 2.5), height 127.8 cm (SDS - 4.6), fathom length 137 cm (SDS < - 3), sitting height 67 cm (SDS < - 3), and sitting height/height ratio 0.489 (SDS - 1.2). Thyroid was nonpalpable, puberty stage was compatible with Tanner stage 3. Her intelligence was normal, she had no neurological disorder, and other systemic examinations were normal. Other laboratory findings of the patient whose serum electrolytes were normal are given in ► Tables 1 and ► 2. Platyspondyly (► Fig. 4a), irregularity in the distal metaphysis, and sclerotic-lucent density changes (► Fig. 4b) were detected on direct radiographs. No calcification was detected in brain computed tomography. Since her cousin (Case 1) had an *ACP5* mutation and had a similar clinical picture, it was seen that she carried the same variant homozygous c.155 A>C (p.K52T) in the genetic test sent.

Discussion

Spondyloenchondrodysplasia was first described by Schorr et al. in 1976 in 2 siblings [6]. SPENCD (OMIM: 271.550) and SPENCDI (OMIM 607944), which were initially thought to be two separate diseases, are



► **Fig. 1** Diffuse thickening of the basement membrane of the glomerulus is seen with enlargement of the capillary network. Black arrows; basement membrane thickening; red stars: enlarged capillary network. Hematoxylin–Eosin staining, 400x magnification, 50 scale bar.

now referred to as SPENCDI since they are now considered as different clinical spectrums of the same disease [1]. SPENCDI is caused by a compound heterozygous or homozygous mutation in the *ACP5* gene encoding the TRAP (tartrate resistant acid phosphatase) protein. Evidence of autosomal dominant inheritance has also been reported [7]. Although TRAP, encoded by the *ACP5* gene, is a lysosomal enzyme, unlike other lysosomal hydrolases, it is secreted only from bone (osteoclasts) and immune system (hematopoiesis monocytic lineage) cells [8, 9]. TRAP downregulates osteopontin by dephosphorylating the extracellular matrix protein osteopontin. It has been shown that patients with SPENCD exhibit higher levels of active osteopontin in serum, urine and dendritic cells, since this down-regulation is not present [10]. Osteopontin functions as a master regulator of bone resorption in osteoclasts and a stimulator of interferon (IFN)-alpha production in plasmacytoid dendritic cells. Dendritic cells with TRAP deficiency due to mutation in the *ACP5* gene secrete Th1-polarizing proinflammatory cytokines such as TNF- α [11, 12]. High osteopontin increases the production of IFN, therefore SPENCDI is included in the type 1 interferonopathy group [13].

SPENCDI is classified as type 4 enchondromatosis [14], and short stature is a constant finding, as in our patients. The degree of short stature may be variable and may only present with severe short stature [15–17]. Short stature has been attributed to non-ossifying lesions affecting the growth plate in long bones and vertebrae [3]. In addition, steroids used for chronic infections and SLE-like diseases also contribute to short stature.

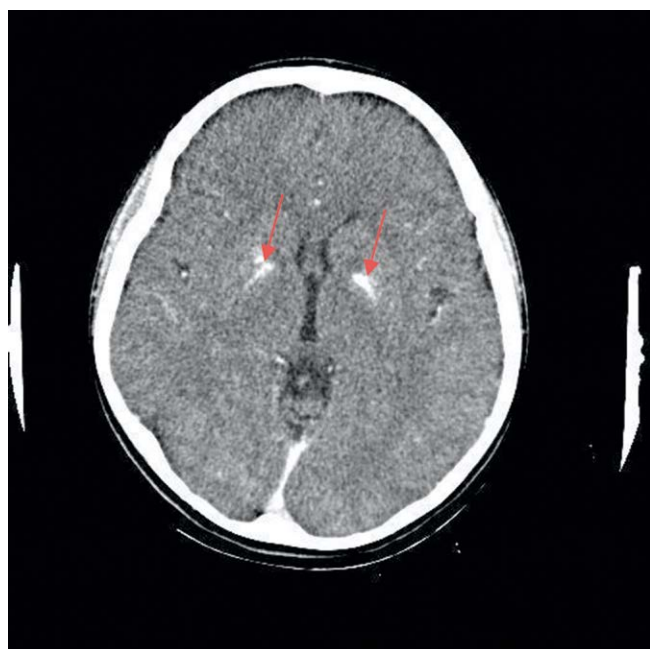
► **Table 1** Hematological and hormonal values of the patients.

	Case 1	Case 2	Reference ranges
Age	10.5	12.5	
Hemoglobin (g/dl)	11.2	10.3	12–15
Leukocyte count (mm ³)	3.690	2.940	4.000–12.000
Neutrophil count (mm ³)	2.280	1.160	2.000–7.000
Lymphocyte count (mm ³)	1.113	1.440	1.700–5.700
CD3 + (T) cell count #	69.9%	51.5%	58–82%
CD3 + -CD4 + T helper cell count #	26.2%	20.4%	26–48%
CD3 + -CD8 + T cytotoxic cell count #	41.3%	28%	16–32%
CD4 + /CD8 + ratio#	0.62	0.73	0.9–3.4
CD19 + (B) cell count#	13.8%	36.4%	10–30%
CD56 + (NK) cell count#	11.4%	8.3%	8–30%
Thrombocyte count (mm ³)	244.000	236.000	100.000–400.000
Free T4 (pmol/L)	14.89	11.67	9–19.04
TSH (mIU/L)	2.55	7.51	0.34–4.9
Vitamin B12 (ng/L)	152	330	187–883
Anti-TPO (IU/ml)	16.84^b	0	0–5.61
Cerebral calcification	Yes	No	
Mental condition	Normal	Normal	
Urine protein/creatinine (mg/g creatinine)	237^a	15	<200

Values outside the reference range are in bold, ^a Nephrotic level proteinuria at first diagnosis. #Reference number 23. ^b Anti-TPO 315.6 IU/ml and Anti-Tyroglobulin 797 IU/ml at the time of first diagnosis; Abbreviations: TSH, Thyroid-stimulating hormone; TPO, Thyroid peroxidase; NK, Natural Killer; CD, Cluster of differentiation.



► **Fig. 2** Increased lumbar lordosis and platyspondyly on lateral thoracolumbar radiograph (2a). Irregularity, sclerotic-lucent density changes in the distal metaphysis of the femur, tibia and radius on direct radiographs (2b, 2c, red arrow).



► **Fig. 3** Bilateral calcification in lentiform nuclei.

Although type I IFN plays an important role in viral infections, excessive type 1 IFN production leads to primary immunodeficiencies or monogenic autoinflammatory disorders [18]. In addition, type I interferons induce autoimmunity by promoting the release of nuclear antigens from dying cells and maturation of autoreactive B cells [19]. The prevalence of autoimmune diseases, especially autoimmune thrombocytopenia, is very high in SPENCDI

patients. Autoimmune disease is found in 92 % of the cases [1]. SLE is the first autoimmune disease defined as associated with increased levels of IFN [20]. Renal involvement with or without SLE was reported at a rate of approximately $\frac{1}{3}$ in SPENCDI patients in two large series [1, 10]. However, at least one of the immunological data related to SLE (ANA, Anti-dsDNA, C3, C4) was positive in all patients evaluated as renal involvement without SLE in these series. Differently, our patient (Case 1) had renal involvement (nephrotic syndrome: membranous nephropathy) without SLE-related immunological or skin findings. In these patients, renal involvement may not be solely SLE-related. It has also been shown that increased osteopontin has an important role in the pathogenesis of albuminuria by acting on renal podocytes, as shown in diabetic patients (possibly increasing glomerular damage through TGF-beta expression) [21]. In addition, since clinical findings may occur at different ages in the same family, even in patients with the same *ACPS5* gene mutation [22], immunological and skin findings related to SLE may occur in our patients in the coming years.

Hypothyroidism in SPENCDI patients may occur by autoimmune and non-immunological (non-immune) mechanisms. Autoimmune hypothyroidism was found in one of our patients (Case 1), while compensated non-immune hypothyroidism was found in the other (Case 2). Although there were no clinical findings such as recurrent viral/bacterial/fungal infections in both of our patients, lymphopenia was evident. In Case 1, there were immunoglobulin values below the reference values, which we can call mild hypogammaglobulinemia. Low lymphocyte counts and/or hypogammaglobulinemia have also been reported in the literature [1, 23, 24]. It has also been observed that low lymphocyte counts may be present in all 3 (T, B, and NK) cell types. In the literature, both a numerical increase and a decrease in CD8⁺ T cells have been reported with low

► **Table 2** Immunological values of the patients.

	Case 1	Case 2	Reference ranges
C3 (g/L)	1.30	1.34	0.90–1.80
C4 (g/L)	0.27	0.21	0.10–0.40
ANA	Negative	Negative	Negative
Anti-dsDNA	Negative	Negative	Negative
IgG (mg/dL) [§]	845	1820	935–1176 * 1066–1218 [#]
IgA (mg/dL) [§]	140	235	95–137 * 99–172 [#]
IgM (mg/dL) [§]	64	101	97–129 * 111–140 [#]
IgE (IU/ml)	191	1990	0–100
Anti-toxoplasma IgG	Negative	Negative	
Anti-HBs	Negative (8,12),	Positive (86,2),	
Anti-CMV IgG	Positive (250)	Positive (250)	
CMV IgG avidity		High avidity (89.5)	
Anti-rubella IgG		Positive (47.59)	
EBV VCA IgG (AU/ml)		Positive (32.6)	

Values outside the reference range are in bold, * Reference range of Case 1, [#]Reference range of Case 2, [§]Reference number 24; Abbreviations: C3, complement C3; C4, complement C4; ANA, Antinuclear antibodies; Anti-dsDNA, Anti-double stranded DNA; Anti HBs, hepatitis B surface antibody; CMV, Cytomegalovirus; EBV VCA, Epstein-Barr virus viral capsid antigen.



► **Fig. 4** Platyspondyly on lateral thoracolumbar radiograph (4a). Irregularity and sclerotic-lucent density changes in the distal metaphysis of the ulna and radius on direct radiographs (4b, red arrow).

CD4, one of the T cell subgroups [1]. Among our cases, the number of CD4+ T cells increased in patient 2, and the number of CD8+ T cells increased in Case 1, and the ratio was reversed, and B and NK cells were found to be normal in both. In fact, both patients had an absolute or relative immune dysregulation due to

CD4+ cell deficiency. This is reflected in the clinic more as autoimmunity. Again, in one of our patients, the capacity to produce natural/specific antibodies against the vaccine (rubella or hepatitis B) and previous infections (CMV, EBV) was normal, while the antibody titer against the hepatitis B vaccine was low in Case 1. IgG was increased in Case 2, and IgG and IgM were slightly decreased in Case 1. Serum immunoglobulin values did not reflect a significant antibody deficiency due to mild/borderline hypogammaglobulinemia. However, as in immune dysregulation disorders, serum IgE was found to be increased in all cases. We can say that the most prominent finding in both of our patients was the numerical deficiency of CD4+ cells.

Central nervous system findings such as spasticity, intracranial calcifications and mental retardation may be seen in some patients with SPENCDI [3, 5]. Although there was no neurological involvement in two of our patients, there was cerebral calcification in Case 1. Since it is stated that cerebral calcifications may start late, intermittent central imaging should be performed in these patients [3].

Conclusion

Endocrinologists, immunologists, rheumatologists, nephrologists and orthopedists should be aware of this syndrome, because SPENCDI causes a pleiotropic (due to more than one phenotypic effect of a gene) clinical picture. In patients with severe short stature accompanied by autoimmune disorders, ACP5 gene mutation should be considered in the differential diagnosis. In addition, in the presence

of early-onset nephrotic syndrome and autoimmune thyroiditis, the patient should be evaluated for this type of monogenic disorders as well.

Informed consent

Informed consent was obtained from the parents of the individuals included in the study.

Conflict of Interest:

The authors have declared that no conflict of interest exists.

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