Pseudoachondroplasia: A Case Report

Vladimir Radlović, Željko Smoljanić, Nedeljko Radlović, Miroslav Jakovljević, Zoran Leković, Siniša Dučić, Polina Pavichević

1University Children's Hospital, Belgrade, Serbia; 2School of Medicine, University of Belgrade, Belgrade, Serbia; 3Child and Youth Health Care Institute of Vojvodina, Novi Sad, Serbia

INTRODUCTION

Pseudoachondroplasia (PSACH) is a form of osteochondrodysplasia with an estimated prevalence of approximately 1/20,000-1/30,000 individuals [1-4]. The basis of the disease forms an autosomal dominant defect in the expression of cartilage oligomeric matrix protein (COMP) caused by a structural mutation in exons 8-19 of COMP gene located on the chromosome 19p12-13.1 [5-8]. The majority of COMP mutations are missense mutations and small in-frame deletions and duplications found in exons 8-14 of this gene encoding the eight calmodulin-like calcium-binding repeats and exons 15-19 encoding the carboxyl-terminal globular domain [9]. The consequence of this defect, characterized by penetrance, is a development of the osteogenic disorder, i.e. the transformation of cartilage into bone tissue followed by typical metaphyseal, epiphyseal and vertebral abnormalities [1, 10]. The main clinical characteristics of the disease are a disproportionate short stature similar to achondroplasia, brachydactyly, short, broad and ulnar deviation of the hands, forearms and lower limbs anomalies, joint hyperlaxity, abnormal gait, exaggerated lumbar lordosis, scoliosis and early onset osteoarthrosis [1, 7-10]. The affected individual has normal length at birth, and generally, growth retardation will not be recognized until late infancy or more frequently between two to three years of age [7-10]. Notably, all patients have normal craniofacial appearance and intelligence [2, 10, 11]. Here, we present a girl with an early expressed and severe PSACH born to clinically and radiographically unaffected parents.

CASE REPORT

A 6.5-year-old girl presented with disproportionate short stature (79.5 cm, <P5; -32% from the average height for the age and gender), short and genu varum lower limbs, abnormal gait, exaggerated lumbar lordosis, short forearms, short, broad and ulnar deviation of the hands, brachydactyly and joint hyperlaxity (Figure 1). Craniofacial appearance and intelligence as well all other physical findings were normal. She was born to clinically and radiographically unaffected and non-consanguineous parents. Her birth weight was 2700 g, length 51 cm and head circumference (HC) 33 cm. According to her parents, the girl was normal until 3 months of age when she expressed growth retardation with apparently shorter extremities in relation to the torso. With age, her rhizomelic dwarfism became increasingly visible, and since completed 15 months of age, when she started to walk, the disease was complicated with genu varum, lumbar lordosis and abnormal gait. Beside visibly short forearms, short, broad and ulnar deviation of the hands, brachydactyly and joint hyperlaxity, the radiographic picture showed markedly flared metaphyses, small and irregular epiphyses and poorly formed acetabulum.

Conclusion

PSACH is an achondroplasia-like rhizomelic dwarfism recognized by the absence of abnormality at birth, normal craniofacial appearance, characteristic epiphyseal and metaphyseal radiographic finding and joint hyperlaxity.

Keywords: pseudoachondroplasia, rhizomelic dwarfism, osteochondrodysplasias
started to walk, the disease was complicated with the genu valgum plus lumbar lordosis and abnormal gait. With age, her longitudinal growth showed the following values: at 17 months 61 cm (-28.5%), at 25 months 65 cm (-29%) and at 4 years 75 cm (-26%). Having in mind a progressive and diagnostically unclear disorder, the child was referred to our institution for additional investigations.

Based on the abovementioned facts, as well as the characteristic radiographic findings, the diagnosis of PSACH was verified (Figures 2A and 2B). The evident signs of osteoarthritis were not seen. Except for decreased serum concentration of 25(OH)D (64 nmol/L) and increased PTH (91.5 pg/ml) at first examination, all other laboratory findings, also including serum calcium, phosphorus and alkaline phosphatase, were normal. With 400 IU of vitamin D and additional intake of milk and milk products, the serum levels of 25(OH)D and PTH were normalized after 3 months. In order to maintain a normal balance of calcium and phosphorus, other than daily consumption of about 500 ml of milk or yogurt, the intake of vitamin D, 400 IU and 200 IU daily during colder and warmer weather periods, respectively, was recommended. Besides the corresponding paediatric and orthopaedic follow-up and adequate physical therapy, the parents were advised not to expose their child to exaggerated physical activities.

**DISCUSSION**

PSACH is a part of osteochondrodysplasias, a group of more than 150 distinct disorders characterized by bone and cartilage maldevelopment [2, 10]. In almost all of patients, it appears to be secondary to autosomal dominant structural mutation within the genes encoding for COMP on the chromosome 19p12-13.1, and is most closely related to multiple epiphyseal dysplasia (MED/EDM1), a disorder also characterized by the mutation of the COMP [7-12].

COMP, also known as thrombospondin 5, is a 757-amino acid or 550 k-Da homopentameric glycoprotein present in the extracellular matrix (ECM) of cartilage, tendon, ligament and smooth muscle [13, 14]. Its presence in the ECM of these tissues is of essential significance for their growth, development and maintenance. As the consequence of this defect, both PSACH and MED chondrocytes retain lamellar and granular appearing material in large rough endoplasmic reticulum cisternae [11]. This material is composed of COMP and other ECM proteins including types II and IX collagens and matrilin-3 [15, 16]. By the method of fluorescence deconvolution analysis, these retained proteins have been recently shown to be organized into the matrix network suggesting that the stalled mutant COMP inappropriately interacts intracellularly with the matrix protein partners [15, 16, 17]. The retention of the intracellular matrix is toxic to the chondrocytes, and induces apoptosis causing the chondrocyte death [17]. The loss of chondrocytes in the growth plate translates, resulting into decreased long bone growth and the disproportionate short stature in PSACH. Additionally, the intracellular retention of the COMP and death of chondrocytes result in loss of these proteins in the ECM [18, 19, 20]. The respective consequence is a disorganized type II collagen network most likely due to the absence of type IX collagen which is needed to crosslink type II collagen [21]. Association of the COMP deficit in the ECM and poorly organized structure of the articular cartilage lead to joint abnormalities and early onset osteoarthritis in patients with the PSACH and MED/EDM1 [20, 22].

The children with PSACH are always normal at birth and its disease usually presents at 2-3 years of age with disturbance in walking and lower limb deformity [7-11]. Over the years, rhizomelic dwarfism becomes apparent
The radiographic features are typical for rhizomelic dwarfism and include shortened bones, more prominent in the proximal than in the distal part, with flared and irregular metaphysial and epiphyseal changes [10, 23]. The most affected long bones are femur and humerus. The bones of the hand and foot are too broad and short with a small and immature epiphysis [23]. The x-ray of the pelvis shows flattened, irregular femoral heads with shortened necks and widened pubic symphysis [7]. The acetabulum is poorly formed with the horizontal roofs. The radiographic features include normal skull and facial bones and variable vertebral findings such as platyspondyly with the anterior beaking of the upper lumbar and lower thoracic vertebrae, lordosis and scoliosis [8, 23]. Differential diagnoses of this radiographic picture in the context of clinical findings include achondroplasia, MED/EDM1 and spondyloepiphyseal dysplasia (SED) congenita [9]. Patients with achondroplasia have disproportionally large head with a prominent frontal region and depressed bridge of the nose. The basic differentiating point is that the epiphyses of patients with achondroplasia are normal. MED/EDM1 is characterized by a near normal pelvis with some scalloping of the acetabular margin. The SED, contrary to PSACH, is typified by hip joints that are affected disproportionately in relation to more distal portion of the lower extremities.

The diagnosis of PSACH is based primarily on personal and family history and characteristic physical and radiographic findings [10, 24, 25]. The finding of decreased serum COMP concentration may be an additional diagnostic marker of PSACH [4, 7, 26]. Whenever possible, genetic verification of the disorder is also done [25]. Therapy of PSACH is reduced to physiotherapy, management of spinal deformities and corrective orthopaedic surgery [25, 27, 28, 29]. Intensive physical activity is recommended. Surgical correction of the limb deformities should be postponed until the end of the growth period [28]. We are presenting a girl who is a typical example of the patient with PSACH. She was born with a normal BL and her appearance was the same as that of any other child with clinically and radiographically unaffected parents. Beside her, the parents have a healthy 12-year-old boy. Mode of PSACH inheritance clearly compels us to draw the conclusion that, in our patient, the disease was the result of newly developed mutation. As the realistic possibility of somatic mutation in the early postconception phase is low, it can be additionally concluded that the cause of PSACH development in this case should be searched in the germline (gonadal) mosaicism of parents [25, 30]. Although PSACH is not generally recognized until late infancy or more frequently between two to three years of age, progressive longitudinal growth retardation of the extremities, as the initial illness sign, was detected in our patient already at age of 5 months [7-10]. In her later years, her disease also manifested other clinical and radiological characteristics, which represented the basis of her diagnostics [10, 24, 25].

Having in mind the age of our patient, as well as the severity of the disease at this stage, treatment was based on adequate paediatric-orthopaedic supervision, physiotherapy and avoiding of intensive physical activity [25, 28]. A suboptimal serum level of 25(OH)D recorded at first examination was corrected. Because of the significance of vitamin D in the calcium and phosphorus homeostasis, as well as the bone tissue itself, the maintenance of vitamin D optimal balance with adequate diet regime should be continued.

In conclusion, PSACH represents a rare form of achondroplasia-like rhizomelic dwarfism recognized by the absence of abnormality at birth, normal craniofacial appearance, characteristic epiphyseal and metaphyseal radiographic findings and joint hyperlaxity. Despite being the AD inherited disorder, it is usually seen as the consequence of a newly developed mutation, i.e. gonadal mosaicism in parents. Therapy is primarily physical-orthopaedic. In addition, the prevention of vitamin D and/or calcium deficit is of exceptional significance, identically to other disorders that can disturb the integrity of bone tissue.

REFERENCES

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1Универзитетска деца клиника, Београд, Србија; 2Медицински факултет, Универзитет у Београду, Београд, Србија; 3Институт за здравствену заштиту деце и омладине Војводине, Нови Сад, Србија

КРАТАК САДРЖАЈ
Увод Псеудоахондроплазија (ПСАХ) је аутозомно доминант- на остеохондроплазија изазвана мутацијом гена који кодира хорсакавачи олигомерни макрилни протеин. Одликују је ризомелни мали раст, деформитети екстремитета и кичменог стуба, хиперпластичност зглооба и рана остеоартроза. Следи приказ девојчице клинички и радиографски здравих родитеља с тешком и рано испољењом ПСАХ.

Приказ болесника Девојчица узраста од шест и по година, нормалног краниофиозацоналног изгледа и интелигенцијипри- мљена је на преглед због диспропорционално малог раста (телесна висина 79,5 cm; <П5; -32%). Заостање у лонгитуди- налном расту са видно краћим екстремитетима у односу на труп уочено је тро месяца по рођењу. Са растом и развојем ризомелни тип ниског раста постајао је све израженији, а од навршених 15 месеци, када је проходала, болест се ком- пликовала са геном вара, лумбалном лордозом и отежа- ним хоханем. Појединачно скраћени надлактица, краћих, пречниках унапредотка ширих, краћих престривих и хи- перпластичних зглооба, на рекенскимнимима су за- паженог могносоме ретивемета, мале неправилне епифизе и словане формирање ацетабулима.

Закључак ПСАХ је облик ризомелничког малог раста налак на ахондроплазију, препознатива по нормалним изгледом на остаћу, непостојаћом краниофиозацоналним поремећаји, типичним епифизометафизарним радиографским налазом и хиперпластичном зглообом.

Кључне речи: псеудоахондроплазија; ризомелнички мали раст; остеохондроплазија