A mild form of pseudoachondroplasia : minimal epi-metaphyseal involvement of long bones

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要約　偽性軟骨無形成症 (PSACH) の診断上の問題は、椎体の特徴的変化が10歳頃に消失し、成人例ではPSACHほど重症ではないMED Fairbank typeと鑑別が困難なことである。我々は、長管骨の骨端骨幹端障害が軽度で慎重がPSACH平均の+2SDで椎体は典型的変化を示す日本人女児を報告する。太く短い指はなく椎体の特徴的変化も消失したため、患児はPSACHのみではなくMED Fairbank typeとも診断されていなかった。分子生物学的にPSACHとMEDの重複が議論されており PSACHの臨床像の拡がりの研究は重要である。

Introduction

Pseudoachondroplasia (PSACH) was first defined as a separate disorder among a group of spondylo-epiphyseal dysplasias in 1959 by Maroteaux and Lamy [1] . The diagnostic criteria include normal skull, disproportionate short stature with normal trunk and short limbs, anterior tongue-like protrusion and biconvexity of the vertebral bodies and epi-metaphyseal dysplasia during growth [2] .

One problem in diagnosing PSACH is that the characteristic changes of the vertebral bodies invariably disappear around the age of 10 [3] . Subsequently, an adult case might be misdiagnosed as MED, Fairbank type, though it is generally believed that the latter is less radiologically severe and that height of the affected individual is greater than in PSACH [3]

We present a case with minimal epi-metaphyseal involvement of long bones in spite of the typical change of the vertebral bodies. Since the overlap between PSACH and MED has recently been discussed from the viewpoint of molecular biology [4,5] , study of the spectrum of clinical features of PSACH is valuable.

Case History

The propositus was a 3-year-old girl (Y.T.) referred for her short stature. There were no relatives with short stature. Her birth weight was 3075 g and she began walking at 20 months. Facial appearance and mental status were normal.

At the age of 3, she was 88 cm tall (+0.1SD of a standard Japanese girl) with an arm span / body height of 0.89. The short limb type of short stature became apparent thereafter, and at the age of 10 her height was 119 cm (-2.5SD) and arm span / body height was 0.92. Among PSACH patients, however, her short stature was not severe ; her height corresponded to +2SD on the growth curve of PSACH by Horton et al. [6] . There was general joint laxity but no gross deformity in extremities including the hands.

Radiographs at age 3 revealed an anterior tongue-like protusion and biconvexity of the vertebral bodies, which are characteristic of PSACH (Fig. 2A) . The epi-metaphyseal abnormalities of the proximal and distal femur and the proximal tibia were minimal from 3 to 10 years in comparison with those in typical PSACH patients during their growth period. Malalignment around the knee joints such as genu varus did not develop during this follow-up period .

Radiographs of the hands showed some epi-metaphyseal abnormalities and shortness of the long bones from 3 to 8 years, but the degree of the abnormalities was less than that of typical PSACH patients ; the epiphyses were not small, the metaphyses were not flared and long bones were not stubby (Fig. 2E) . There was also no delay in development of the carpal bones at the age of 3 and 8 in this case, unlike the

typical PSACH patients .

Discussion

PSACH is known to vary widely in severity. Short stature is not apparent untill 3 years of age, and thereafter the growth curve deviates from the standard. Deviation in this case was less than that of typical PSACH, the smallest among our 16 patients with this affliction from 3 to 10 years of age, and +2SD on the PSACH growth curve at 10 years. The radiological changes in this case were also milder than those of typical PSACH in spite of the typical vertebral change ; the epiphyses are not too small, the metaphyses are not too flared and shortness of the long bones is not as apparent from 3 to 10.

McKeand et al. [7] reported that 84 percent of PSACH patients have bowleg deformity, which develops after walking begins and advances between 5 and 15 years of age [8] . In this mild form, no malaligment around the knee joints was seen from 3 to 10 years.

These physical and radiological findings are less severe than those reported as mild form in the literature [9, 10] except for one reported by Maroteaux et al [11] . Although one problem in making a diagnosis of PSACH is that the mild form of an adult case might be misdiagnosed as MED, Fairbank type, the cases reported by Maroteaux et al. and this one by us might not have been diagnosed only as PSACH but also even as MED, Fairbank type after the typical changes of the vertebral bodies had disappeared.

The overlap between PSACH and MED has been discussed ; Maroteaux et al. (1980) [11] and Stanscu et al. (1982) [12] reported the accumulation of abnormal materials in rough endoplasmic reticulum in cartilage cells in patients with PSACH and similar ultrastructural findings were found in the severe form of MED, Fairbank type in 1993 [13] . More recently it has been shown that mutation in COMP gene causes both PSACH and MED [5] , and PSACH and MED, Fairbank type, were also shown to be allelic disorders [4, 5] . These molecular and genetic findings suggest the importance of determining the spectrum of clinical features of PSACH. This case is important because it shows the mildest end of the reported spectrum. The presence of such a mild form as described here also means that in evaluating the results of genetic molecular findings we should pay attention to the clinical evidence on which the diagnosis is made.

References

1) Maroteaux P, Lamy M. Les formes pseudoachondroplasiques des dysplasies spondylopiphysaires. Press Med 1959 ; 67 : 383-386.

2) Hall JG. Pseudoachondroplasia. In : Bergsma D ed. Birth Defects Compendium New York : The National Foundation-March of Dimes, Alan R. Liss, Inc., 1979 ; 889-890.

3) Wynne-Davies R. Atlas of skeletal dysplasias. Churchill Livingstone : Edinburgh, 1985.

4) Rimoin DL, Rasmussen IM, Briggs MD, Roughley PJ, Gruber HE, Warman ML, Olsen BR, Hsia YE, Yuen J, Reinker K, Garber AP, Grover J, Lachman RS, Cohn DH. A large family with features of pseudoachondroplasia and multiple epiphyseal dysplasia ; exclusion of seven candidate gene loci that encode protein of the cartilage extracellular matrix. Human Genetics, 1994 ; 93 : 236-242.

5) Briggs MD, Hoffman SM, King LM, Olsen AS, Mohrenweiser H, Leroy JG, Mortier GR, Rimoin DL, Lachman RS, Gaines ES, Cekieniak JA, Knowlton RG, Cohn DH. Pseudoachondroplasia and multiple epiphyseal dysplasia due to mutations in the cartilage oligimeric matrix protein gene. Nat Genet, 1995 ; 10 (3) : 330-336.

6) Horton WA, Hall JG, Scott CI, Pyeritz RE, Rimoin DL. Growth curves for height for diastrophic dysplasia, spondyloepiphyseal dysplasia congenita, and pseudoachondroplasia. Am J Dis Child, 1982 ; 136 : 316-319.

7) McKeand J, Rotta J, Hecht JT. Natural history study of pseudoachondroplasia. Am J Med Genet, 1996 ; 63 : 406-410.

8) Kopits SE. Orthopedic complication of dwarfism : Clin Orthop, 1976 ; 114 : 153-179.

9) Wynne-Davies R, Hall CM, Young ID. Pseudoachondroplasia. clinical diagnosis at different ages and comparison of autosomal dominant and recessive type. A review of 32 patients (26 kindred) . J Med Genet, 1986 ; 23 : 425-434.

10) Maloney FP, Hall JG, Crossman M, Wadia R, Dorst JP. Four types of pseudoachondroplastic spondyloepiphyseal dysplasia. Birth Defects Orig Art Ser, 1969 ; 5 th/4 : 242-259.

11) Maroteaux P,Stanescu V, Fontaine G. The mild form of pseudoachondroplasia. Eur J Pediatr, 1980 ; 133 : 227-231.

12) Stanescu V, Maroteaux P, Stanescu R. The biochemical defect of pseudoachondroplasia. Eur J Pediatr, 1982 ; 138 : 221-225.

13) Stanescu R, Stanescu V, Muriel MP, Maroteaux P. Multiple epiphyseal dysplasia, Fairbank type. Morphologic and biochemical study of cartilage. Am J Med Genet, 1993 ; 15. 45 (4) : 501-507.

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