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ORIGINAL ARTICLE

Criteria for radiologic diagnosis of hypochondroplasia in neonates

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Abstract
Background A radiologic diagnosis of hypochondroplasia is hampered by the absence of age-dependent radiologic criteria, particularly in the neonatal period.
Objective To establish radiologic criteria and scoring system for identifying neonates with fibroblast growth factor receptor 3 (FGFR3)-associated hypochondroplasia.
Materials and methods This retrospective study included 7 hypochondroplastic neonates and 30 controls. All subjects underwent radiologic examination within 28 days after birth. We evaluated parameters reflecting the presence of (1) short ilia, (2) squared ilia, (3) short greater sciatic notch, (4) horizontal acetabula, (5) short femora, (6) broad femora, (7) metaphyseal flaring, (8) lumbosacral interpedicular distance narrowing and (9) ovoid radiolucency of the proximal femora.
Results Only parameters 1, 3, 4, 5 and 6 were statistically different between the two groups. Parameters 3, 5 and 6 did not overlap between the groups, while parameters 1 and 4 did. Based on these results, we propose a scoring system for hypochondroplasia. Two major criteria (parameters 3 and 6) were assigned scores of 2, whereas 4 minor criteria (parameters 1, 4, 5 and 9) were assigned scores of 1. All neonates with hypochondroplasia in our material scored ≥6.
Conclusion Our set of diagnostic radiologic criteria might be useful for early identification of hypochondroplastic neonates.

Keywords Achondroplasia · FGFR3 · Hypochondroplasia · Neonate · Radiography · Radiologic diagnosis · Scoring system

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Introduction

Hypochondroplasia is the mildest form of fibroblast growth factor receptor 3 (FGFR3)-associated skeletal dysplasia with an incidence of about 1 in 50,000 [1]. Affected individuals usually present after 2 years of age and seek medical help at preschool age because of mild body disproportion and short stature. A diagnosis of hypochondroplasia rests on the presence of several distinctive radiologic findings, such as broad long bones, lumbosacral interpedicular distance narrowing, short femoral necks and elongation of the fibula [2, 3]. However, the diagnosis of hypochondroplasia is hampered by the absence of age-dependent radiologic criteria, particularly in the neonatal period. It has been reported that younger affected children are not definitively diagnosed with hypochondroplasia [4].

We previously reported two cases of hypochondroplasia in children with FGFR3 mutations, focusing on prenatal ultrasonography findings in the third trimester and postnatal radiologic findings [5]. These children had short femora with increased biparietal diameter in utero; however, they were not diagnosed with hypochondroplasia in the neonatal period. The final diagnosis was made at the age of 3 years, when they visited our clinic because of short stature. Upon retrospective radiologic review, we learned that the radiologic findings relevant to hypochondroplasia were apparent in the neonatal period and that radiologic diagnosis may have been even easier in the neonatal period than in early childhood. The manifestations related to the ilia and proximal femora were particularly useful. The identification of short, squared ilia with short greater sciatic notches and horizontal acetabula along with the ovoid radiolucency of the proximal femora mimicking that of achondroplasia warranted the diagnosis.

The present study is dedicated to radiologic features in hypochondroplastic neonates with FGFR3 mutations and quantitative measurements that facilitate definitive diagnosis. We propose radiologic criteria for the identification of hypochondroplasia in the neonatal period.

Materials and methods

Subjects included seven hypochondroplasia neonates with FGFR3 mutations, three term neonates with nonsyndromic fetal growth restriction, and 30 term control subjects with available results of radiologic examination within 28 days after birth. All hypochondroplasia neonates underwent radiologic examination in the neonatal period, such as partial skeletal survey or chest and abdominal radiographs, because of short femoral length on fetal ultrasonography or clinically suspected disproportionate micromelia. Control subjects and individuals with nonsyndromic growth restriction were hospitalized from 2010 to 2014 and were born after 36 weeks of gestation. They did not have major congenital anomalies, and they underwent radiologic examination with extension position of hip joint and knee joint because of transient tachypnea of the newborn, meconium aspiration syndrome or suspected neonatal infection. We hypothesized that skeletal changes in the pelvic bones, femora and lumbar spine, which were seen in achondroplasia, were most useful for the diagnosis of hypochondroplasia. Accordingly, we calculated eight parameters and monitored one radiologic sign: (1) ratio of maximal transverse diameter of the ilia to its maximal longitudinal diameter (assessment of short ilia), (2) iliac angle (squared ilia), (3) length of the greater sciatic notches (short greater sciatic notch), (4) acetabular angle (horizontal acetabula), (5) ratio of femoral length (FL) to body length (femoral shortening), (6) ratio of diameter of the femoral mid-shaft to femoral length (broad femora), (7) ratio of width of the distal femoral metaphysis to femoral length (metaphyseal flaring), (8) ratio of interpedicular distance of the L1 vertebra to that of L4 (lumbosacral interpedicular distance narrowing) and (9) presence or absence of ovoid radiolucency of the proximal femora. Measurement procedures are illustrated in Fig. 1.

The open-source OsiriX software dedicated to the analysis of Digital Imaging and Communications in Medicine (DICOM) images (http://homepage.mac.com/rossetantoine/osirix) was

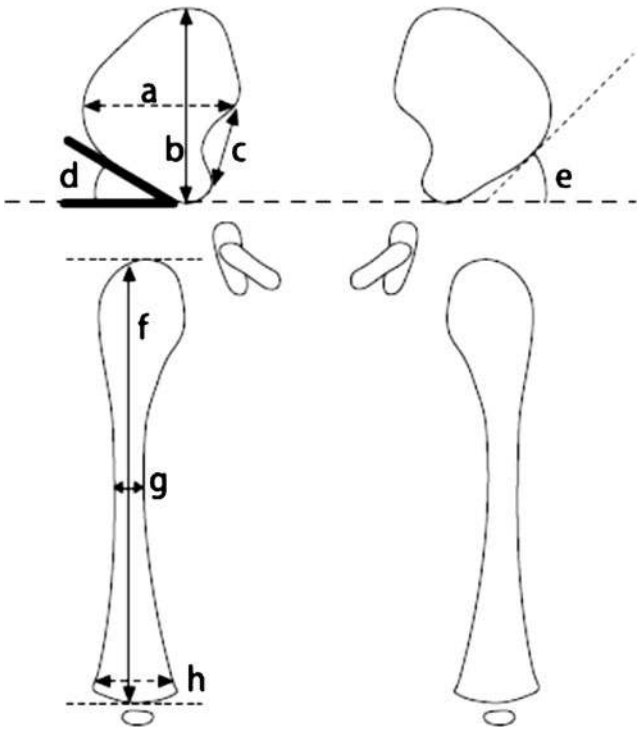

Fig. 1 Diagrams illustrate the measurements based on radiologic findings. The dotted line connects the bottom ends of the ilia: **a** maximal transverse iliac diameter, **b** maximal longitudinal iliac diameter, **c** greater sciatic notch, **d** acetabular roof angle, **e** iliac angle (formed by the tangent line of iliac wing with dotted line), **f** femur length, **g** mid-femur width, **h** maximal distal width of the femur

used for performing measurements. Only radiographs taken with the hip and knee joints extended and without significant joint rotation were analyzed.

Statistical significance of differences between control subjects and hypochondroplasia subjects was analyzed with the Mann–Whitney *U* test. A *P*-value<0.01 was considered significant. All analyses were performed with JMP, version 10.0 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the Institutional Review Board Committee at Niigata University School of Medicine, and informed consent was given by the parents or guardians of the patients with hypochondroplasia.

Results

Clinical manifestations of hypochondroplasia are summarized in Table 1. All the subjects with hypochondroplasia showed low femoral length and biparietal diameter at or above the higher limit of the normal range on prenatal ultrasonography. The results of the Shapiro-Wilk W test showed that all the measurement parameters in the control group followed the Gaussian distribution. The measurement parameters for short ilia, short greater sciatic notch, horizontal acetabula, short femora and broad femora (parameters 1, 3, 4, 5 and 6) were statistically different between the hypochondroplasia and control groups ($P<0.01$), while the remaining parameters were not. Parameters 3, 5 and 6 did not overlap between the 2 groups, while parameters 1 and 4 did (Fig. 2). To distinguish subjects with hypochondroplasia from control subjects, we defined the following cut-off values based on the differences of at least 2 standard deviations from the average values in the control group: >0.80 for parameter 1, <7.5 mm for parameter 3, <22° for parameter 4, <0.14 for parameter 5 and >0.10 for parameter 6. Although assessment of ovoid radiolucency of the proximal femora was somewhat subjective, careful interpretation confirmed its presence in 6 out of 7 children with hypochondroplasia (Fig. 3). There were no abnormalities in other bones.

Based on these results, we defined a tentative scoring system for the diagnosis of hypochondroplasia (Fig. 4). The 2 major criteria (parameters 3 and 6 – short greater sciatic notch and broad femora) were assigned scores of 2. In addition, 4 minor criteria (parameters 1, 4, 5 and 9) were assigned scores of 1 for the following reasons: (a) femoral shortening (parameter 5) was a nonspecific finding; (b) short ilia and acetabular angle (parameters 1 and 4) showed overlaps between the hypochondroplasia neonates and normal controls and (c) the results of the assessment of ovoid radiolucency (parameter 9) were interpreter-dependent. Because all 7 neonates with hypochondroplasia showed combined scores of 6 points or more (Table 2), we presumed that a total score of 6 points or higher warrants thinking about a diagnosis of FGFR3-associated hypochondroplasia. We applied this scoring system to 30 control subjects and the 3 neonates with nonsyndromic growth restriction. The corresponding total scores were less than two in all these cases.

Discussion

It was previously believed that the diagnosis of hypochondroplasia was difficult to establish in infancy. However, recent in utero identification of short femora on prenatal ultrasonography has led to several reports on the early diagnosis of hypochondroplasia [6–10]. It has been found that discrepancy in growth between femoral length and biparietal diameter in the third trimester is highly indicative of this disease [5, 9, 11]. The final diagnosis of hypochondroplasia is established based on the molecular analysis of the FGFR3 gene. This test, however, is relatively expensive and a reliable radiology-based scoring system would be highly beneficial.

Table 1 Genetic and clinical manifestations in 7 children with hypochondroplasia

Child	1	2	3	4	5	6	7
FGFR3 mutation	L324V	N540K	N540K	N540K	S351C	N540K	N540K
Femur length standard deviation score in last trimester	−2.1	−2	-	−3.3	−3.3	−3.5	−2.7
Biparietal diameter standard deviation score in last trimester	0.3	1.3	-	3.3	0.3	3	1.8
Gestational age (weeks) at birth	38	40	38	38	39	38	39
Birth weight (g)	2,780	3,270	2,603	3,102	3,146	2,936	3,228
Birth length (cm)	45.5	49	44.5	49	47	46	45.5
Sex	M	M	F	F	M	F	M
Age at diagnosis[a]	3y 6 m	3y 6 m	1 m	2y	1y 7 m	1 m	1 m

M male, *F* female

[a] The diagnosis was based on the radiologic findings

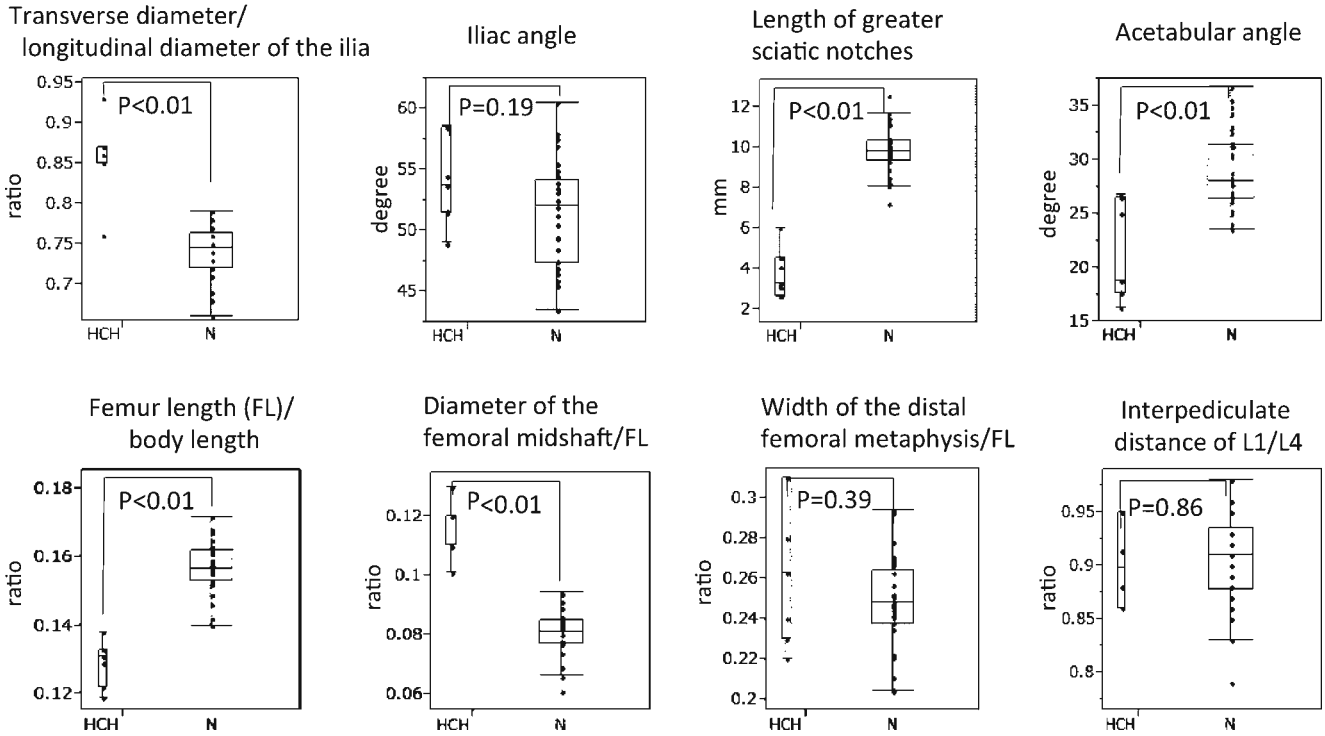

Fig. 2 Results of the measurements in 30 controls and in 7 children with hypochondroplasia. The bottoms and tops of the boxes correspond to the first and third quartiles, respectively, and the horizontal lines inside the boxes indicate the median values. Boxes show as follows: (1) Ratio of maximal transverse diameter to maximal longitudinal diameter of the ilia, (2) iliac angle, (3) length of the greater sciatic notches, (4) acetabular angle, (5) ratio of femoral length to body length, (6) ratio of diameter of the femoral mid-shaft to femoral length, (7) ratio of width of the distal femoral metaphysis to femoral length and (8) ratio of interpediculate distance of L1 to L4. Parameters 1, 3, 4, 5 and 6 were significantly different between the hypochondroplasia and control groups ($P<0.01$). *HCH* hypochondroplasia, *N* control group

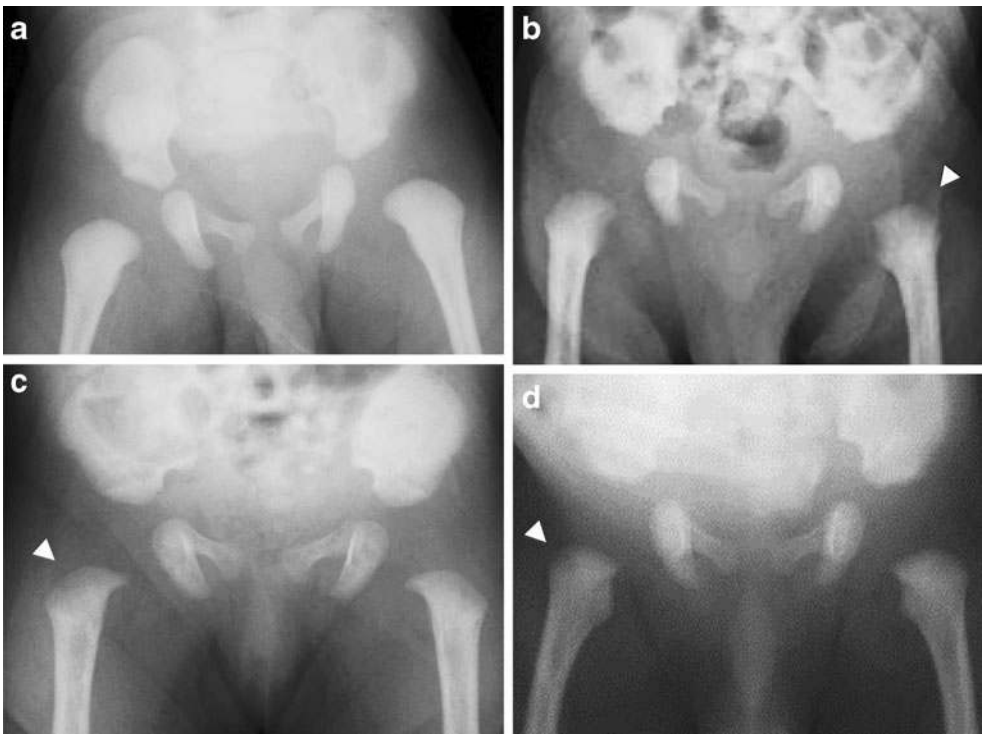

Fig. 3 Ovoid radiolucency of the femoral neck in anteroposterior radiographs. **a** A child in the control group; **b** Child 5 in the hypochondroplasia group (male neonate); **c** Child 6 in the hypochondroplasia group (female neonate); **d** Child 7 in the hypochondroplasia group (male neonate). An ovoid lucency (*arrowheads* in **b-d**) is seen in the femoral neck of the children with hypochodroplasia. All the subjects underwent radiologic examination in the neonatal period.

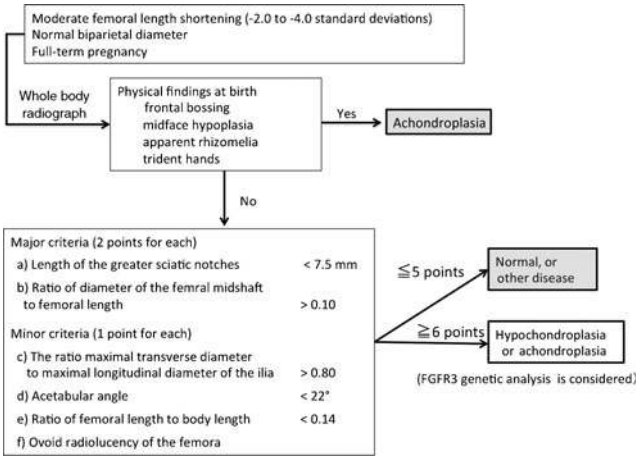

Fig. 4 Proposed flow chart for diagnosis of hypochondroplasia in the neonatal period

In this study, we used radiologic measurements of the ilia and femora to verify that hypochondroplastic neonates had short ilia with short greater sciatic notches and short, broad long bones. Furthermore, ovoid radiolucency of the proximal femora, which reflects the scooped-out appearance of the proximal femoral metaphysis typical of achondroplasia, was always discernible. Horizontal acetabula were also evident, but their presence was inconsistent among the hypochondroplasia neonates. In contrast, although lumbosacral interpedicular distance narrowing is an important diagnostic sign in childhood, it was not useful in our neonatal patients.

Identification of cases with mildly shortened femoral length has become more common with the widespread utilization of fetal ultrasonography. Such cases indicate the presence of mild bone dysplasia exemplified by hypochondroplasia, chromosome disorders such as trisomy 21, and nonsyndromic or syndromic fetal growth retardation (FGR). Although still tentative, our diagnostic criteria might be useful for the differentiation between hypochondroplasia and nonsyndromic growth restriction. Moreover, the radiologic changes in neonates with hypochondroplasia are relatively mild, and their identification may be difficult for nonexperts in bone dysplasias. This emphasizes the potential value of the measurement parameters proposed in the present study.

However, our scoring system is based on nonspecific skeletal changes, such as iliac hypoplasia, a scooped-out appearance of the proximal femora and short, broad femora; thus, it does not enable one to distinguish hypochondroplasia from other skeletal dysplasias, including mild achondroplasia [12]. The final radiologic diagnosis should depend on the overall pattern recognition and other distinctive skeletal changes. For example, cartilage hair hypoplasia causes a diagnostic difficulty in the neonatal period, as does hypochondroplasia [13]. However, mild femoral bowing and round distal femoral epiphyseal ossification warrant a diagnosis of cartilage hair hypoplasia. Molecular diagnoses are essential in difficult cases. To be essential, our scoring system would be utilized as screening for mild neonatal skeletal dysplasias.

The relatively small number of subjects is also a limitation of this study. Furthermore, all measurements were obtained in term neonates; it is currently unknown whether these data are applicable to premature neonates. Finally, correct positioning (extended hip and knee joints without joint rotation) is essential for obtaining interpretable measurements. Further studies in a larger population of hypochondroplasia, including premature neonates, are warranted to validate these criteria for the diagnosis of hypochondroplasia.

Conclusion

We propose a set of diagnostic radiologic criteria that can be useful for early identification of hypochondroplastic neonates.

Table 2 Application of the new scoring system to 7 neonates with hypochondroplasia

Parameter	Child	1	2	3	4	5	6	7
3	Short greater sciatic notches	2	2	2	2	2	2	2
6	Broad femora	2	2	2	2	2	2	2
1	Short ilia	1	1	1	1	1	1	0
4	Horizontal acetabula	1	1	0	1	0	1	0
5	Femoral shortening	1	1	1	1	1	1	1
9	Ovoid radiolucency of the femoral neck	1	0	1	1	1	1	1
Total score		8/8	7/8	7/8	8/8	7/8	8/8	6/8

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Compliance with ethical standards

Conflict of interest None

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