Original Article

DOI: 10.5582/irdr.2020.01019

Health assessment of patients with achondroplasia, pseudoachondroplasia, and rickets based on 3D non-linear diagnostics

Jian Zhang[1,2,§], Yanqin Lu[1,2,§,*], Yanzhou Wang[3], Tianyou Li[3], Chuanming Peng[1,2], Shie Zhang[1,2], Qingxia Gao[2], Wei Li[2], Chunshang Liu[2], Jinxiang Han[1,2,*]

[1] School of Medicine and Life Sciences, University of Jinan, Shandong Academy of Medical Sciences, Ji'nan, China;
[2] Key Laboratory for Biotech Drugs of the National Health Commission, Key Laboratory for Rare & Uncommon Diseases of Shandong Province, Shandong Medicinal Biotechnology Centre, Shandong First Medical University & Shandong Academy of Medical Sciences, Ji'nan, China;
[3] Shandong Provincial Hospital Affiliated with Shandong First Medical University, Ji'nan, China.

SUMMARY The goal of this study was to analyze diminishment of the functional status of the skeleton, parts of organs, regions of the brain, connective tissues, and chondrocytes in patients with achondroplasia (ACH), pseudoachondroplasia (PSACH), and rickets. Three-dimensional non-linear scanning (3D-NLS) was used to analyze the functional status of patients with genetic bone disorders, including 7 patients with ACH, 3 patients with PSACH, and 3 patients with rickets. Results indicated that the percentage of patients with long bones in the decompensatory phase did not differ depending on whether they had ACH, PSACH, or rickets. Joints in the decompensatory phase did not differ in patients with ACH except for the right hip (16.67%). Various joints were in the decompensatory phase (16.7-33.3%) in patients with rickets. The thoracic vertebrae, lumbar vertebrae, and liver were in the decompensatory phase in all 3 groups of patients. Connective tissues were in the decompensatory phase in 33.33% of patients with ACH. None of the patients with PSACH had chondrocytes in the decompensatory phase but 66.67% of patients with ACH or rickets did. Regions of the brain in the decompensatory phase were most prevalent in patients with rickets or ACH but not in patients with PSACH. In conclusion, diagnosis based on 3D-NLS was able to identify the functional status of genetic bone disorders. Some areas of decompensation were common to the 3 diseases studied but other areas were specific to a given disease.

Keywords achondroplasia, pseudoachondroplasia, rickets, health assessment, 3-D non-linear scanning technology

1. Introduction

Since three-dimensional non-linear scanning (3D-NLS) was first used in diagnostics in the late 90s, it has made significant progress thanks to the introduction of new technologies and new facilities (*1*). A clinical examination with 3D-NLS and the resulting diagnosis are based on a three-dimensional reconstruction combined with spectral-entropy analysis (SEA) of the scanned site. This technique is more visual and accurate than conventional methods in many cases, such as diagnosis of degenerative-dystrophic damage to intervertebral discs (*2*), damage to the ankle (*3*), and screening for potential vascular pathologies (*4*).

Achondroplasia (ACH, MM:100800), also known as chondrodysplasia fetalis or chondrodystrophic dwarfism, is an autosomal-dominant genetic disorder. Its incidence is between one in 77,000 and one in 15,000 (*5*). Its clinical features include an enlarged head, frontal bossing, short limbs, and trident hands. All of these features can be found at birth. Other features, such as limited elbow extension, tibial bowing, and thoracolumbar kyphosis, may also be present (*6,7*).

Pseudoachondroplasia (PSACH, MIM 177170) is another autosomal-dominant genetic disorder. It is clinically characterized by a normal head and face, lordotic lumbar spine, and epiphysis and metaphysis where epiphyseal development is delayed and metaphyses widen (*8*). It might be accompanied by symptoms of tibial bowing and early osteoarthritis due to a non-concentric load (hips and knees) (*9,10*).

Rickets is a group of heterozygous diseases caused either by a vitamin D deficiency (*11*) or dominant (*12*) or recessive genetic disorders (*13,14*). Its clinical features include delayed fontanelle closure, beading of the ribs and a pigeon chest, scoliosis, lumbar lordosis, bowed legs, muscle weakness, and metaphyseal changes that result in thickening of the wrists and ankles and even deformity of the hips (*15*).

The aim of this study was to use 3D-NLS to evaluate the functional status of the skeleton, parts of organs, regions of the brain, connective tissues, and chondrocytes in patients with ACH, PSACH, and rickets and to analyze the biochemical equilibrium between damage to organs, tissues, and cells and pathological changes.

2. Materials and Methods

2.1. Patients

This study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the Shandong Medicinal Biotechnology Centre (No. 2016-04). Informed consent was provided by all patients or their guardians. This study included 7 patients with ACH (five were 2-6 years of age, one was 23 years of age), 3 patients with PSACH (two were 3 years of age and one was 10 years of age), and 3 patients with rickets (3, 4, and 28 years of age, respectively). All patients were diagnosed clinically.

2.2. Health assessment

The functional status of target areas, including the skeleton (long bones and joints), regions of the brain (frontal lobes, parietal lobes, temporal lobes, and occipital lobes), parts of organs (heart, liver, kidneys, and lungs), connective tissues, and chondrocytes, was evaluated in patients diagnosed with ACH, PSACH and rickets using the "Metatron"-4025 system (IPP, Russia) equipped with high-frequency digital trigger sensors (4.9 GHz). The health assessment was graded according to the following functional statuses: good health, standard health, self-repair, start of decline, and excessive damage or a critical state. Whether patients with ACH, PSACH, and rickets were in a compensatory phase (good health, standard health, or self-repair) or a decompensatory phase (start of decline or excessive damage or a critical state) of their disease was analyzed and compared.

3. Results

3.1. Functional status of the skeleton

Figure 1 shows that the percentage of patients with long bones in the decompensatory phase did not differ among the 3 groups of patients. The functional status of joints (Figures 2 and 3) in the decompensatory phase did not differ for patients with ACH (66.67%) except for the right wrist or for patients with PSACH. The percentage of patients with joints in the decompensatory phase differed in patients with rickets: the shoulder was in the decompensatory phase in 33.33%, the right wrist was in the decompensatory phase in 33.33%, the right hip was in the decompensatory phase in 16.67%, and the ankle was in the decompensatory phase in 33.33%.

Figure 3 shows that the percentage of patients with cervical vertebrae in the decompensatory phase did not differ depending on whether they had ACH or PSACH, but it did differ (66.67%) in patients with rickets. The thoracic vertebrae were in the decompensatory phase in 16.67% of patients with ACH, 100% of patients with PSACH, and 33.33% of patients with rickets.

The lumbar vertebrae were in the decompensatory phase in 83.33% of patients with ACH, 50.00% of patients with PSACH, and 66.67% of patients with rickets. The sternum was in the decompensatory phase in 50.00% of patients with ACH or PSACH but did not differ in patients with rickets.

3.2. Functional status of parts of organs

The left lobe of the liver was in the decompensatory phase in 50.00% of patients with ACH, 100.00% of patients with PSACH, and 33.33% of patients with rickets while the right lobe of the liver was in the decompensatory phase in 66.67% of patients with ACH, 50.00% of patients with PSACH, and 33.33% of patients with rickets (Figures 4 and 5).

The percentage of patients with the heart or left kidney in the decompensatory phase did not differ among the 3 groups of patients, but the right kidney was in the decompensatory phase in 16.67% of patients with ACH, 0% of patients with PSACH, and 33.33% of patients with rickets. The lungs were in the decompensatory phase in 16.70% of patients with ACH but did not differ in patients with PSACH or rickets. The left hilum was in the decompensatory phase in 83.33% of patients with ACH, 50.00% of patients with PSACH, and 66.67% of patients with rickets, while the right hilum was in the decompensatory phase in 50.00% of patients with ACH, 100% of patients with PSACH, and 100% of patients with rickets.

3.3. Functional status of tissues and cells

The functional status of connective tissues and chondrocytes is shown in Figure 5. Connective tissues were in the decompensatory phase in 33.33% of patients with ACH. The percentage of patients with chondrocytes in the decompensatory phase did not differ in patients with PSACH but it did differ (66.67%) in patients with ACH or rickets.

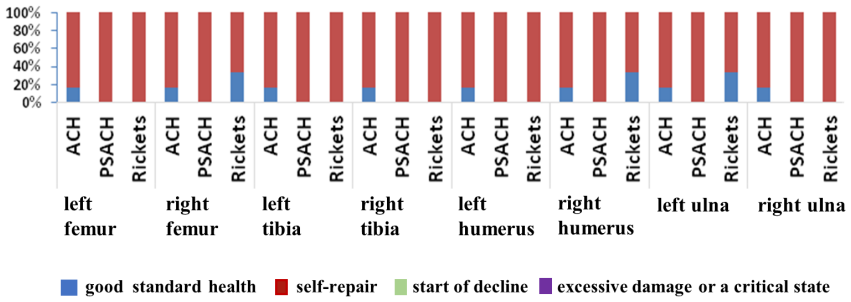

Figure 1. Functional status of long bones

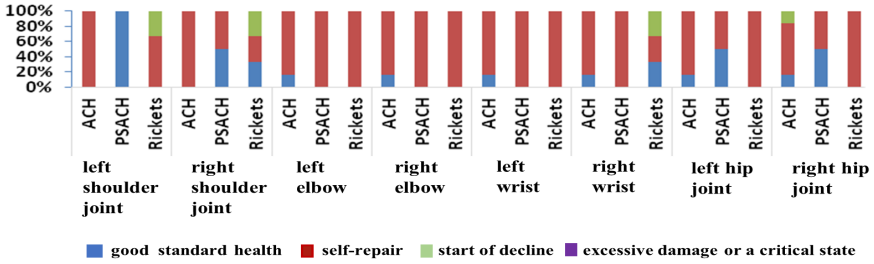

Figure 2. Functional status of joints

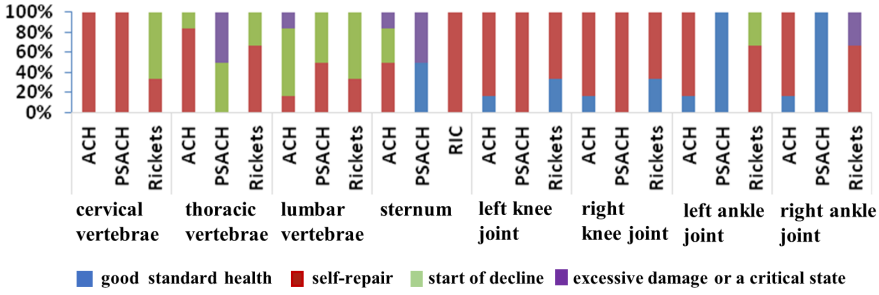

Figure 3. Functional status of parts of the spine and joints

Figure 4. Functional status of parts of organs

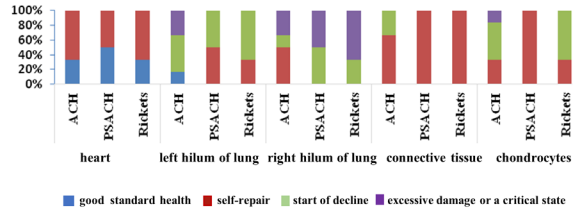

Figure 5. Functional status of parts of organs, connective tissue, and cartilage

3.4. Functional status of the brain

The functional status of regions of the brain is shown in Figure 6. The left frontal lobe and right parietal lobe were in the decompensatory phase in 33.33% of patients with rickets. The right frontal lobe, right temporal lobe, and medulla oblongata were in the decompensatory phase in 16.67% of patients with ACH. The left temporal lobe and left occipital lobe were in the decompensatory phase in 50.00% of patients with ACH, 0% of patients with PSACH, and 33.33% of patients with rickets.

The percentage of patients with the left frontal lobe and right occipital lobe in the decompensatory phase did not differ among the 3 groups of patients.

4. Discussion

Three-D NLS is able to depict pathological areas

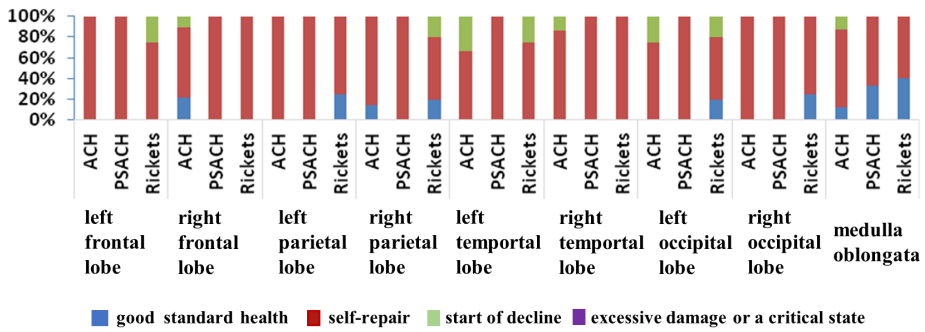

Figure 6. Functional status of cerebral regions

through reconstruction of three-dimensional high-resolution images of scanned sites. It offers accurate positioning and real-time information, and its sensitivity is comparable to that of computed tomography (CT) (*4*). In addition, it is cheap, simple, and non-invasive.

When diagnosing cholangiocarcinoma in patients with intrahepatic cholangiectasis, 3D-NLS compensates for the indistinct location according to conventional non-invasive methods such as ultrasound scanning, magnetic resonance imaging (MRI), and CT and it avoids injury to the human body by an invasive examination, such as endoscopic retrograde cholangiopancreatography (*16*).

The current study graded and quantitatively analyzed the functional status of the skeleton, regions of the brain, parts of organs, connective tissues, and chondrocytes. The percentage of patients with long bones in the decompensatory phase did not differ depending on whether they had ACH, PSACH, or rickets. The percentage of patients with the shoulder, right wrist, or ankle in the decompensatory phase differed in patients with rickets. The results agreed with clinical features such as swelling of joints like the wrists and ankles (*17*). The right hip was in the decompensatory phase only in patients with ACH, which might be related with the square-shaped ileum, small sacroiliac notches, or other clinical features of ACH (*17*). A markedly higher percentage of patients with ACH had thoracic vertebrae and lumbar vertebrae in the decompensatory phase compared to the other 2 groups. This was consistent with the thoracolumbar kyphosis characteristic of ACH (*18,19*). Decompensation in the thoracic spine of patients with PSACH was correlated with abnormal spine development (*20*). A relatively high percentage of patients with ACH had connective tissues and chondrocytes in the decompensatory phase; this is presumably related to the clinical manifestations of muscle hypotonia and soft tissue laxity, which might be responsible for thoracolumbar kyphosis. The liver was in the decompensatory phase in over 1/3 of patients with ACH, PSACH, or rickets. The hilum of the lungs was in the decompensatory phase in over half of the patients with ACH, PSACH, or rickets. The long bones were normal while the thoracic and lumbar vertebrae were affected in all the groups of patients. Abnormalities of the wrists and ankles in patients with rickets differed from those in patients with ACH or PSACH. The hips of patients with ACH differed from those in patients with the other two diseases.

In conclusion, all 3 of the diseases studied involved skeletal dysplasia with similar clinical features. As described here, 3D-NLS offers a new avenue to accurate differential diagnosis. A limitation of this study was the small sample of patients with PSACH or rickets. Therefore, these 3 diseases need to be studied further. In summary, 3D-NLS is potentially an alternative method with which to diagnose genetic bone disorders.

Acknowledgements

This work was supported by a grant from the Shandong Government (2016GSF201222, 2015ZRC03171, 2016ZDJS07A10). The authors wish to thank all of the patients who participated in this study.

References

1. Nesterov V. Main tendencies of non-linear technology development. Acta Medica Medianae. 2013; 52:41-44.
2. Nesterov VI. CT and 3D NLS-diagnostics of degenerative-dystrophic damages of intervertebral discs. Kerala Journal of Orthopaedics. 2013; 26:110-112.
3. Nesterov V. MRI and NLS-diagnostics of ankle joint damages. Kerala Journal of Orthopaedics. 2013; 26:67-69.
4. Vagulin VM, Patrushev SM, Nesterov VI. 3D NLS-method in vascular pathology diagnosis. CorSalud. 2013; 5:237-239. (in Spanish)
5. Baujat G, Legeai-Mallet L, Finidori G, Cormier-Daire V, Le Merrer M. Achondroplasia. Best Pract Res Clin Rheumatol. 2008; 22:3-18.
6. Carter EM, Davis JG, Raggio CL. Advances in understanding etiology of achondroplasia and review of management. Curr Opin Pediatr. 2007; 19:32-37.
7. Hoover-Fong J, McGready J, Schulze K, Alade AY, Scott CI. A height-for-age growth reference for children with achondroplasia: Expanded applications and comparison with original reference data. Am J Med Genet A. 2017; 173:1226-1230.
8. Posey KL, Hayes E, Haynes R, Hecht JT. Role of TSP-5/COMP in pseudoachondroplasia. Int J Biochem Cell

Biol. 2004; 36:1005-1012.
9. Posey KL, Alcorn JL, Hecht JT. Pseudoachondroplasia/ COMP - Translating from the bench to the bedside. Matrix Biol. 2014; 37:167-173.
10. Unger S, Hecht JT. Pseudoachondroplasia and multiple epiphyseal dysplasia: New etiologic developments. Am J Med Genet. 2001; 106:244-250.
11. Glorieux FH, Pettifor JM. Vitamin D/dietary calcium deficiency rickets and pseudo-vitamin D deficiency rickets. Bonekey Rep. 2014; 3:524.
12. Balsan S, Tieder M. Linear growth in patients with hypophosphatemic vitamin D-resistant rickets: Influence of treatment regimen and parental height. J Pediatr. 1990; 116:365-371.
13. Feng JQ, Ward LM, Liu S, *et al.* Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet. 2006; 38:1310-1315.
14. Lorenz-Depiereux B, Schnabel D, Tiosano D, Hausler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. Am J Hum Genet. 2010; 86:267-272.
15. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics. 2008; 122:1142-52.
16. Shvack AY, Kuznetsova TG. Lopukhov GA. Three-dimensional non-linear diagnostics of cholangiocarcinoma in patients suffering from intrahepatic cholangiectasis. Actual Aspects of NLS-Diagnostics. 2013; 1:8-12.
17. Ohata Y, Ozono K. Updates on rickets and osteomalacia: Guidelines for diagnosis of rickets and osteomalacia. Clin Calcium. 2013; 23:1421-1428.
18. Kumar CP, Song HR, Lee SH, Suh SW, Oh CW. Thoracic and lumbar pedicle morphometry in achondroplasia. Clin Orthop Relat Res. 2007; 454:180-185.
19. Khan BI, Yost MT, Badkoobehi H, Ain MC. Prevalence of scoliosis and thoracolumbar kyphosis in patients with achondroplasia. Spine Deform. 2016; 4:145-148.
20. McKay SD, Al-Omari A, Tomlinson LA, Dormans JP. Review of cervical spine anomalies in genetic syndromes. Spine (Phila Pa 1976). 2012; 37:E269-277.

Received February 17, 2020; Revised February 25, 2020; Accepted February 28, 2020.

[§]These authors contributed equally to this work.

**Address correspondence to:*
Yanqin Lu and Jinxiang Han, Shandong First Medical University & Shandong Academy of Medical Sciences, 18877 Jingshi Road, Ji'nan, China 250062.
E-mail: yanqinlu@yahoo.com, mls_hanjx@ujn.edu.cn