Three Cases of Familial Clavicular Hypoplasia

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Abstract: CCD (cleidocranial dysplasia) is a kind of rare congenital skeletal dysplasia and deformity. It has rare clinical syndrome, such as forehead radius, small maxilla ofacial, wide long distance eye, collapse nose, widening cranial suture, incompletely closure of the frontal, clavicle hypoplasia, increased range of shoulder motion and other abnormalities. Often accompanied by teeth hypoplasia or impacted, through a careful observation of the clinical morphology, case history and X-ray examination can confirm the diagnosis.

Key words: Skull, clavicular, hypoplasia.

1. Introduction

The rare autosomal dominant congenital skeletal dysplasia and deformity of CCD (cleidocranial dysplasia) is a rare clinical syndrome. The incidence rate is about 1:1,000,000 [1-3], which can be a family clustering disease or can be distributed. The sporadic cases are about 1/3, and there is no significant difference between men and women [4]. It mainly affects intramembranous osteogenesis and cartilage osteogenesis, resulted extensive dysplasia of the entire body, with forehead radius, small maxillofacial region, wide eyelid distance, collapsed bridge of the nose, widened cranial suture, incomplete closure of the frontal fontanelle, and incomplete clavicle. The range of shoulder joints motion is abnormal [5]. It is often accompanied by incomplete or impacted teeth. Studies have confirmed that the CCD gene is a specific gene called runt-related transcription factor 2 (RUNX2).

The RUNX2 gene [6, 7], which encodes a protein which can promote the differentiation of osteoblasts and chondrocytes, it is important for the normal growth and development of bones. However, haploinsufficiency caused by RUNX2 gene mutation is the main cause of CCD [5].

We can usually confirm the diagnosis by carefully observing the clinical form, asking history, and X-ray examination.

2. Clinical Data

The symptoms of skull clavicular dysplasia are a rare autosomal dominant hereditary skeletal systemic disease. The outpatient was a 4 years old boy , with a small face, but his skull looked large. The distance of his eyes is farther than normal boy. The area of the fontanelle was about 0.04 m x 0.04 m. Both sides of the clavicle are shorter than normal clavicle, perhaps half of the normal length. His shoulders slid significantly, and the distance between his shoulders is closer than that of normal boys. The boy’s teeth are irregularly arranged. The boy’s intelligence is normal. There is a relatively large area of scar on the boy's chest skin. The area is about 1.6 centimeter × 1.6 centimeter. This is caused by postoperative hemangioma. This time we examined the trace elements and routine blood test for the children. Conventionally, his calcium and zinc values are in the lowest range of the normal range, the value of iron is normal, and routine blood test is within the normal range. His father had agreed the doctor to examine the skull of the child when his son was 2 years old. The CT results show that the brain of the children is normal, no hydrocephalus, but there is a larger area of skull defects, because the parents are afraid of surgical risk, so they did nothing to protect the open brain. Therefore, now we suggest that his parents should
wear a helmet as soon as possible to protect the exposed brain tissue and prevent accidental collision of external forces. At the same time, fortunately, the children are generally in good healthy condition. His intelligence does not lag behind the same age children.

The boy's father is also a patient of CCD, but his intelligence has developed normally. This father is 36 years old, but when his father as a children, his fontanelle was also relatively large. When at the age of 14 his fontanelle gradually became smaller. Now the size of his father's fontanelle diameter is about like the little finger, his height is 1 point 6 meter. He also has the same physical characteristics, such as his shoulders fell significantly, and his shoulders are shorter than normal man. His father's teeth are irregularly arranged. At the same time, the boy's 59-year-old grandmother like his grandson also has the same clinical performance. Her intelligence is also normal. But fortunately the appearance of the boy's aunt is normal. The main reason may be that the child's great-grandfather and great-grandmother were sister. None of the above three cases has obvious neurological symptoms.

3. Discussion

These three family reports suggest that the development of the skull is a genetic disorder. CCD (cleidocranial dysplasia) is a rare autosomal dominant hereditary disease with occasional recessive inheritance. It is a very rare systemic bone development disorder and odontogenic disease. The pathological manifestations are intramembranous osteogenesis impediments and cartilage developmental disorders. The lesions can affect all of the body's internal cartilage bones. The autosomal dominant causative gene CBFA1/RUNX2 of this disease is located at 6p21 and it is a transcription factor which can activate osteoblast differentiation. It is called CBFA1 (abbreviation for core binding factor α1 or RUNX2) and it is the only gene known to be associated with CCD. The normal form of CBFA1, which encodes cathepsin K, a lysosomal cysteine protease, cathepsin K is a cysteine protease lysosomal protein that is involved in the degradation of bone and cartilage. The formation of bone and cartilage. The RUNX2 protein contains the following domains: Runt domain-DNA binding domain, nuclear localization signal domain, three transcription activation domains, RUNX2 transcription repression domain, and CCD patients may be caused by gene mutations that lead to any structural abnormalities in the RUNX2 protein.

So far in China, 71 cases have been reported from 17 families, and the largest one is from the 5 generations and there were 19 cases. Both males and females are affected. The clinical manifestations include dental abnormalities including delayed deciduous teeth, delayed teeth, excessive teeth and permanent teeth eruption, as well as poor skull development, disproportionately increased head size, widened cranial suture, and insufficient development of paranasal sinus in some patients. They had large head and small face, prominent forehead, wide eye distance, protruding eyes, etc. small face, dentate profile, and due to insufficient development of maxillofacial, pharyngeal cavity, some patients may be complicated by respiratory apnea syndrome. Some patients may suffer from cognitive impairment due to extensive subcapsular cerebral softening under the skull. Some patients present with long neck, clavicle regeneration or developmental disorders, sagging shoulders, tapered chest, short stature, short extremities and fingers, delayed second ossification center of the wrist or second metacarpal development, scoliosis, multiple spina bifida, thorax conical, The ribs lean downward, showing chicken breast, small pelvis, ischium, pubic bone defect or ossification delay, wide pubic symphysis, and enhanced brittleness. Tibial dysplasia, flat acetabulum, large femoral neck, large iliac crest, weak muscles, normal mental development, X-ray showed increased bone density, osteopetrosis, osteolysis of the distal phalanx. The
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Clinical manifestations of patients in the same family are also very different [5, 7]. Most of the free thyroxine and thyrotropin tests were normal. Franceschi [8] reported one CCD family that was misdiagnosed as rickets in three generations [3]. Therefore, patients with atypical symptoms cannot be diagnosed by clinical examination and imaging. Further gene sequence analysis, CMA (chromosomal microarray analysis) or CNV (copy number variations) analysis are required. To further confirm the diagnosis [9] to avoid delaying the patient's condition and missing the best opportunity for treatment. Studies have confirmed that the CCD causative gene is encoded by osteoblast-specific transcription factor (RUNX2). The RUNX2 gene [10], which encodes a kind of protein which can promote the differentiation of osteoblasts and chondrocytes, is important for normal bone growth and development. In 1995 Feldman et al. [10] conducted a continuous analysis of 5 CCD families, including 24 patients and 20 non-patients. Microsatellite markers of two candidate genes on chromosomes 8P and 6 were used. The results showed that the BMP6 gene is located on chromosome 6 and BMP6 is mapped to human 6P based on the homology of mouse and human, and therefore BMP6 is used as a candidate gene for CCD. As an osteoblast-specific transcriptional regulator, RUNX2 has the effect of inducing osteoblast differentiation and promoting the maturation of chondrocytes. Therefore, RUNX2 is important for the maintenance of normal bone growth. For example, like osteoblasts, RUNX2 can promote the specific differentiation of mesenchymal stem cells into osteoblasts and up-regulate the expression of OC (osteocalcin), while promoting the type I collagen, OPN (osteopontin), The synthesis of extracellular matrix such as BSP (bone sialoprotein) and fibronectin promotes mineralization. The RUNX2 of the mice is knockouted, then it completely lacked bone tissue in vivo and exhibited complete bone loss due to loss of cartilage internalization and intramembranous bone function. RUNX2 also plays an important role in cartilage formation and endochondral ossification. RUNX2 is highly expressed in the former hypertrophic chondrocytes and hypertrophic chondrocytes, the expression of which increases with the maturation of chondrocytes and is most pronounced in the terminal stage of hypertrophic chondrocytes [11].

Clinical manifestations of the same family may also different from each other. This different phenotypic may be related to mutations which are located in different functional domains of the RUNX2 gene and have different effects on gene function, or may be related to environmental factors and epigenetics.

4. Conclusions

When we see CCD patient we should suggest them to consider RUNX2 gene mutation for genetic diagnosis. There are some specific treatment principles for CCD: (1) Timely removal of retained deciduous teeth, supernumerary teeth and permanent teeth, and removal of eruption resistance; (2) Improve maxillofacial deformity, restore beauty and function; (3) The patient for adult can use an implant or restoration to restore occlusal function; (4) Protect exposed brain tissue when necessary. (5) Take into account the patient's age, the desired treatment cycle, and the patient's desired therapeutic effect.

References


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