A Female With Angelman Syndrome and Unusual Limb Deformities

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Received 3 May 2004; accepted 7 February 2005. Available online 3 May 2005.

This report presents the case of a 13-year-old female with Angelman syndrome caused by 15q11-13 microdeletion demonstrating unusual marked limb deformities with generalized osteoporosis, delayed bone age, and brachydactyly type B. The radiographs of her femur, tibia, fibula, ulna, and radius revealed curved deformities in the distal diaphysis-metaphysis areas and generalized osteoporosis. This can be explained by the patient’s severe disability, delayed puberty, presumed nutritional and environmental deficits, or rickets. In addition, she had shortening of the distal phalanges of all fingers, the absence of some epiphyses of the distal phalanges, and hypertrophic and curved III metacarpal bones. These clinical findings could not be explained by classical rickets or osteoporosis, but can be classified as brachydactyly type B. To our knowledge, such marked limb deformities and brachydactyly have not previously been described in patients with Angelman syndrome.
Introduction

Angelman syndrome is characterized by severe developmental delay, speech impairment, movement or balance disorder, and behavioral uniqueness [1]. Angelman syndrome is caused by a variety of genetic alterations involving the 15q11-13 region as de novo maternal deletions, mutations of the maternal UBE3A gene, imprinting defects, and paternal uniparental disomy of chromosome 15 [2]. All of these mechanisms lead to the absence of a functional maternal copy of UBE3A, and it has been demonstrated that mutations in this gene may cause Angelman syndrome [3]. However, the phenotype of patients with Angelman syndrome caused by 15q11-13 deletion is more pronounced [4], supporting the hypothesis that other genes in this region may play a role in the modification of the Angelman syndrome phenotype.

Patients with Angelman syndrome frequently manifest delayed or disproportionate growth in head circumference during the early years of life, and many of them become microcephalic [5] and [6]. However, delayed skeletal maturation and dentition associated with general postnatal growth failure are rarely reported [6] and [7]. The incidence of scoliosis and joint contractures increases with age, and these complications are often associated with advanced spasticity [8].

This study describes a 13-year-old female with Angelman syndrome caused by 15q11-13 deletion who possesses unusual marked limb deformities, generalized osteoporosis, delayed bone age, and brachydactyly type B.

Case Report

The patient was born at term after a normal pregnancy and delivery. Her birth weight was 3690 gm, length 51 cm, and head circumference 36 cm. During the first months of life she was irritable and had difficulty sleeping. She began to sit at 9 months, pulled herself to a standing position at 13 months, but she never began to walk independently. The patient was evaluated at the age of 21 months in the children’s clinic because of developmental delay and lack of speech. She underwent full clinical investigation without significantly abnormal results, and her bone age was equivalent to 14 months of age. Her karyotype was normal (46,XX). The cause of her developmental delay at that time remained unclear.

The patient was once again referred to the hospital at the age of 13.3 years because of a marked developmental delay and severe limb deformities. On examination her weight was 22 kg (−3 S.D.) and head circumference 51.5 cm (−2 S.D.). Her height was not measurable as a result of severe limb deformities. Facial features included prognathia, wide mouth, wide-spaced milk teeth, a protruding tongue, and low hairline. On the forehead there was a pigmented spongy formation with a diameter of 3 cm (Fig 1). She had fair skin and light-colored eyes. There was no breast development; she had few pubic hairs. She exhibited brachydactyly: her fingers were short and wide, especially the thumb and first toe. She had a marked generalized resting tremor, an intentional tremor, and truncal ataxia. Her tendon reflexes were slightly exaggerated with no pathological reflexes, and her muscle tone was considered normal. She had no speech, and frequently displayed spontaneous attacks of laughter. Her intelligence quotient according to Griffiths scale was 11.
Figure 1. The patient at the age of 13.3 years. Note the prognathia, wide mouth, widely spaced milk teeth, protruding tongue and low hairline, pigmented spongy formation on the forehead, and marked limb deformities.

X-ray investigations of all of the long bones, hips, and the lumbar region of her spine demonstrated generalized osteoporosis. The femur, tibia, fibula, ulna, and radius manifested curved % in the distal diaphysis-metaphysis areas. The compact layer possessed marked changes of rebuilding, the epiphyses were dysmorphic, and the epiphyseal lines were porous (Fig 2). Her bone age was 8.1 years according to Tanner-Whitehouse radius, ulna, and short bones score (TW-RUS). The distal phalanges of all of her fingers were short. The left hand lacked the epiphyses of the distal phalanges of the II, III, and V fingers, and the right hand lacked the epiphyses of the distal phalanges of the III and V fingers. On both hands the III metacarpal bone was hypertrophic with a curve to the palmar side (Fig 3).

Figure 2. X-rays of the patient: (a) curved deformities in the distal diaphysis-metaphysis areas of the ulna and radius, (b) of the femur, tibia, and fibula; generalized marked osteoporosis.

Figure 3. Short distal phalanges of all fingers, absent epiphyses of the distal phalanges of the II, III, and V fingers on the left hand and of the III and V fingers on the right hand; hypertrophic III metacarpal bones with a curve to the palmar side of both hands.

Genetic investigations were as follows. A deoxyribonucleic acid methylation test for Angelman syndrome indicated absence of the maternal 15q11-13 region; fluorescent in situ hybridization analysis revealed 15q11-13 microdeletion, which confirmed the diagnosis of Angelman syndrome in this patient. The biochemical results were as follows: normal ionized calcium 1.18 mmol/L (normal range, 1.17–1.29), mildly decreased phosphorus 1.01 mmol/L (normal range, 1.1–2.0), and slightly elevated parathyroid hormone 8.72 pmol/L (normal range, 1.5–8.1). Her alkaline phosphatase was elevated 1179.0 U/L (normal range, 70–300). Markers of bone formation (bone alkaline phosphatase isoenzymes 888.3 U/L [normal range, < 140] and osteocalcin 149.8 ng/mL [normal range, 11–43]) and markers of bone resorption (desoxypyridinoline creatinine ratio 40 nmol/mmol [normal range, 4.2–35.7] and C-
telopeptide 1.93 ng/mmol (normal range, 0.025–0.573) were all elevated, indicating rapid bone turnover. The serum 25-hydroxyvitamin D₃ level of 2.4 µg/L (normal range, 9.0–37.6) was significantly reduced. The excretion of phosphorus and calcium in urine were within normal limits. The serum quantitative amino acids analysis was normal, and there was generalized hyperaminoaciduria in the urine. The syphilis rapid plasma reagin (RPR) latex test was negative.

**Discussion**

The patient was a 13-year-old female with Angelman syndrome caused by 15q11-13 deletion, who possesses unusually marked limb deformities with generalized osteoporosis, delayed bone age, and brachydactyly type B. Radiographs of the femur, tibia, fibula, ulna, and radius disclosed curved % in the distal diaphysis-metaphysis areas. The distal phalanges of all fingers were short, some epiphyses of the distal phalanges were absent, and in both hands the III metacarpal bone was hypertrophic with a curve to the palmar side. To our knowledge, the association of Angelman syndrome and marked limb deformities as well as brachydactyly has not previously been reported.

The scabbard-like lower limb deformities in this patient resembled the changes associated with congenital syphilis, but the syphilis rapid plasma reagin latex test was negative.

Bone mass accumulation and longitudinal growth of bone are complex processes controlled by genetic and environmental factors as well as hormonal signals. Indeed, classical rickets should be suspected in any patient with chronic neurodevelopmental disability. This patient had delayed puberty, which also has a negative effect on bone mass accumulation. The most likely cause of her biochemical changes is vitamin-D-deficient rickets. However, the rickets could not explain the entire spectrum of bone alterations in the patient.

The clinical manifestations of scoliosis or kyphosis are consistently described in the independent series of Angelman syndrome patients and appear to become more pronounced or visible with advancing age [6], [8] and [9]. These features could be nonspecific and are relatively common in adults with other severe developmental disabilities, related mostly to decreased mobility and wheelchair dependence. However, the fact that these features were present in several independent series of Angelman syndrome patients in different age groups indicates the possibility that scoliosis and kyphosis are clinical features of Angelman syndrome probably explainable by genetic factors.

The patients with Prader-Willi syndrome, which is the well-known sister syndrome to Angelman syndrome, frequently develop osteoporosis and scoliosis at any age, and kyphosis in early adulthood [10]. Osteoporosis in Prader-Willi syndrome is thought to originate from the combination of decreased production of sex or growth hormones or long-standing hypotonia. Interestingly, in Prader-Willi syndrome both bone mineral content and bone mineral density tend to be reduced, especially in the limbs [11] and [12]. It is plausible that in both syndromes a certain gene or genes are responsible for bone formation and mineralization.

Shortening of the distal phalanges of all fingers and the absence of some epiphyses of the distal phalanges in our patient can be classified as brachydactyly type B, typically characterized by the absent or hypoplastic terminal portions of digits II-V of the hands or feet [13]. Our patient also had hypertrophic curved III metacarpal bones, probably caused by asymmetric shortening of other metacarpal bones, which is also typical to brachydactyly type B [13].

Brachydactyly may be either sporadic, a part of an isolated familial brachydactyly, or a feature of various skeletal dysplasias or genetic syndromes [13]. At least 345 syndromes and skeletal dysplasias with brachydactyly have been described, including Prader-Willi syndrome [14]. Small hands and feet are often cited as a manifestation of Prader-Willi syndrome, but
the shortening of the hands and feet have not been specified [15]. To our knowledge, brachydactyly or shortening of the hands and feet has not previously been described in the case of Angelman syndrome. In the patient described herein, the brachydactyly is probably a sporadic finding. However, we cannot rule out the possibility that this feature is more frequent in Angelman syndrome patients.

Absolute or relative microcephaly is another frequent symptom of Angelman syndrome [1], [5] and [6]. Head circumference is usually normal at birth, but head growth decelerates during the early years of life (the first year), and many individuals with Angelman syndrome become microcephalic. Several typical Angelman syndrome features such as mid-face hypoplasia, prognathism, and delayed and disturbed dentition had been explained by brain development abnormality or behavioral phenotype [16], although these features may just as likely be consequences of abnormal bone maturation.

At present there is one gene, ubiquitin protein ligase E3A (UBE3A) gene, which is known to play an important role in the development of the characteristic clinical phenotype of Angelman syndrome [3]. UBE3A encodes an E6-associated protein (E6-AP)—one of the enzymes of the ubiquitin proteasome degradation pathway [17]. Recently, research has demonstrated that E6-AP possesses two separable independent functions—a ubiquitin protein ligase and a coactivator for the nuclear hormone receptor superfamily [18]. Coactivators with additional enzymatic activity are thought to play an important role in regulating the magnitude of the biological response to steroids, vitamin D, and retinoids in different tissues or individuals. Nawaz et al. [18] found that in the majority of the examined Angelman syndrome patients, the ubiquitin protein ligase function of E6-AP was defective, whereas the coactivator function was intact. However, there is a possibility that gross or complete deletions of E6-AP can result in defective steroid receptor coactivation in tissues where E6-AP is expressed in an imprinted manner. To our knowledge, there are no available data of UBE3A expression in bone tissue. It is likely that defective function of UBE3A/E6-AP influences organ growth including bone formation and mineralization, or the severity of manifestation of rickets.

In conclusion, this is the first report of Angelman syndrome with extraordinary limb deformities. The generalized osteoporosis can be explained by the patient’s severe disability, delayed puberty, and presumable nutritional and environmental deficits. However, short distal phalanges, absent epiphyses of distal phalanges, and the peculiarity of the III metacarpal bones cannot be explained by the above-mentioned causes or rickets, and can be classified as brachydactyly type B. To our knowledge, such marked limb deformities and brachydactyly have not previously been described in patients with Angelman syndrome. Considering that patients with Angelman syndrome have problems with bone maturation, delayed dentition, microcephaly, scoliosis, and kyphosis, it is possible that one or more genes causing Angelman syndrome play a role not only in the development and maturation of the brain, but also in the process of bone formation.

We thank Dr. Inna Justus for careful evaluation of the patient’s radiographs and the family of our patient for their kind cooperation. This study was supported by TARLA 0475, DARLA 1864, and GARLA 4620.

References


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