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Case Report

The third patient with Tsukahara-Azuno-Kaiji syndrome with type A1 brachydactyly, dwarfism, microcephaly, scoliosis, intellectual disability, ptosis, and hearing loss ☆

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ABSTRACT

We report the case of the third patient with Tsukahara-Azuno-Kaiji syndrome. It is characterized by brachydactyly A1, dwarfism, microcephaly, scoliosis, intellectual disability, ptosis, and hearing loss. The first patient was reported in 1989, and the second in 2010. The present patient had many features in common with the previous 2 patients, with a few minor differences. Although this combination of symptoms is very characteristic, the clinicians should know about this syndrome to diagnose it. The syndrome in this patient appeared sporadically, and chromosome G-banding revealed a normal female karyotype of 46XX. However, further genetic research could not be performed. Steady accumulation of information will enable us to discover the true clinical and genetic nature of the disease and to make the diagnosis more easily.

Background

Since the first report of Tsukahara-Azuno-Kaiji syndrome published by Tsukahara, Azuno, and Kaiji in 1989 [1], only one additional case report has been published in over 3 decades [2]. This paper presents the third case of this syndrome. This syndrome is different from the Giuffre-Tsukahara syndrome, which has the peculiar finding of radioulnar synostosis and was reported in 1995 [3].

Case report

The patient was of pure Japanese descent. She was the second child, born via normal vaginal delivery at 40 weeks of gestation. Birth weight, height, and head circumference were 2,350 g, 46.0 cm, and 30.8 cm, respectively (ranging between -2.5 and -3.0 standard deviation [SD] of the Japanese cohort). On day 2, she was transferred to a general hospital because of muscular hypotonia, and poor suckling, and presence of other anoma-

☆ Competing interests: None.

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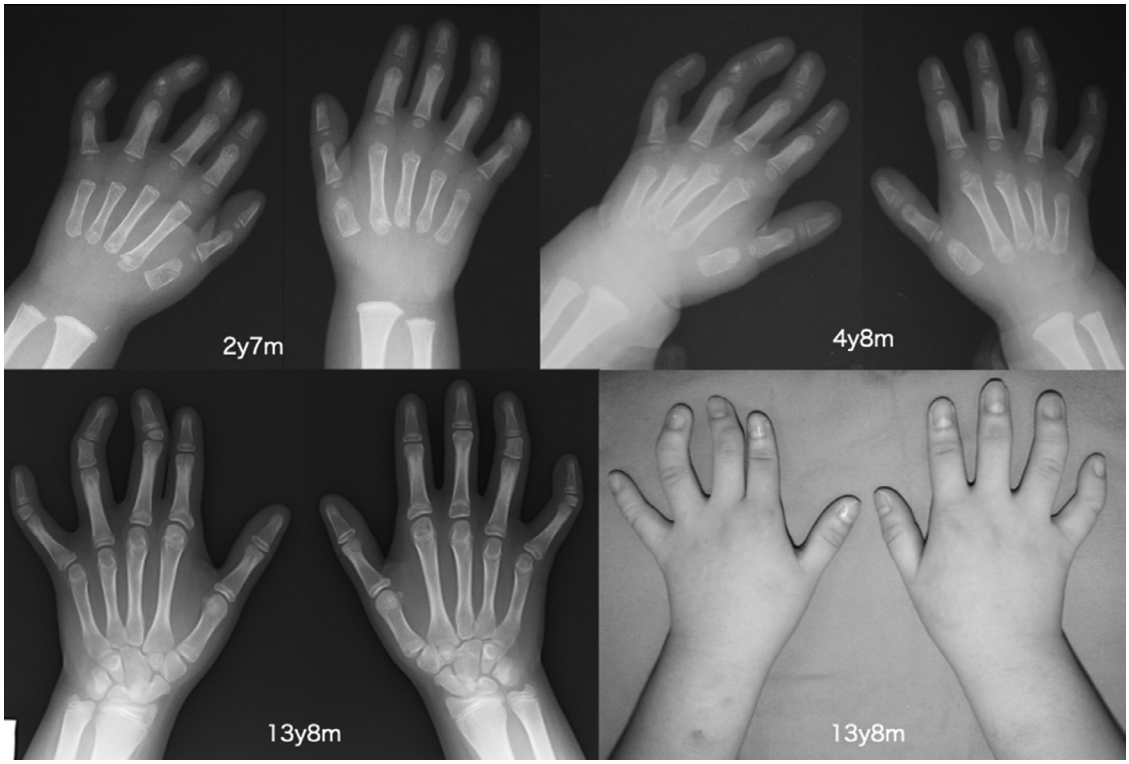

Fig. 1 – Clinical appearance and radiographs of the patient's hands. The carpal bones were not ossified in early childhood. All middle phalanges were aplastic or dysplastic in brachydactyly type-A1 pattern.

lies was suspected. Physical examination revealed ocular albinism and an atrial septal defect. Chromosome G-banding revealed the karyotype of a normal female (46XX). The parents had a nonconsanguineous marriage, and they denied the existence of similar cases among their relatives.

When she was 6 months old, she was referred to the author's center for psychomotor developmental delay. Physical therapy was started at that time, and speech therapy was initiated at age 2 years and 7 months. Head control was achieved at 6 months of age. The patient started walking at age 2 years and 6 months, and 2-word sentence communication began at age 2 years and 9 months.

She had a short stature and microcephaly. She also had flexible flat small feet, small hands with brachydactyly of all fingers, and clinodactyly of both the 4th and 5th fingers. Plain X-ray at age 2-3 years showed absence of ossification of carpal bones, severe dysplasia or deficit of intermediate phalanges of the second to fifth fingers, bowed forearm bones (radius and ulna), and bilateral hip dysplasia (Figs. 1 and 2). Deformed intermediate phalanges caused clinodactyly. She was referred to a podiatrist for her dwarfism. Pituitary hormone secretion was normal. A proper diagnosis was not established in her early childhood, and the outpatient visits were voluntarily ended after she entered elementary school.

She visited the center again at age 10 years because of scoliosis (Fig. 3). However, when brace treatment was recommended, the patient was lost to follow-up again. The third visit was 2 years later; at this time, she was 13 years old. Her scoliosis had worsened, and she and her parents wished for surgical intervention. At this point, she was finally diagnosed with Tsukahara-Azuno-Kaiji syndrome following a simple web search using keywords like brachydactyly, short stature, scoliosis, and so on.

She had most features of Tsukahara syndrome including brachydactyly type A1 (BDA1) with short stature, thoracic scoliosis, microcephaly, ptosis, hearing loss, and mental retardation. Hearing loss was very mild, and there was a history of chronic tympanitis (otitis media) that had caused eardrum perforation. This perforation had healed naturally.

Radiologically, in addition to BDA1 and thoracic scoliosis, she had bilateral hip dysplasia, coxa valga, and short and bowed radius and ulna. Her hands and feet were small and had symphalangisms. She also had sandal gaps but hallux abducto valgus made them unnoticeable. She did not have syndactyly of bony or soft tissue in her hands and feet.

Other previously reported facial features, such as epicanthic folds, upslanting palpebral fissures, myopia, long philtrum, and a bulbous nose with anteverted nares, were all found in this patient, except for persistent pupillary membranes.

She had mild intellectual disability. Her intelligence quotient was evaluated as 51 at age 7 years and 4 months, and 53 at age 14 years and 6 months. She had interpersonal problems and often had trouble with her classmates at school. Surgery was performed for scoliosis at age 15 years and 8 months. Her final height was 141 cm at age 17 years and 10 months, which is below the -3.0 standard deviation of the average for Japanese girls.

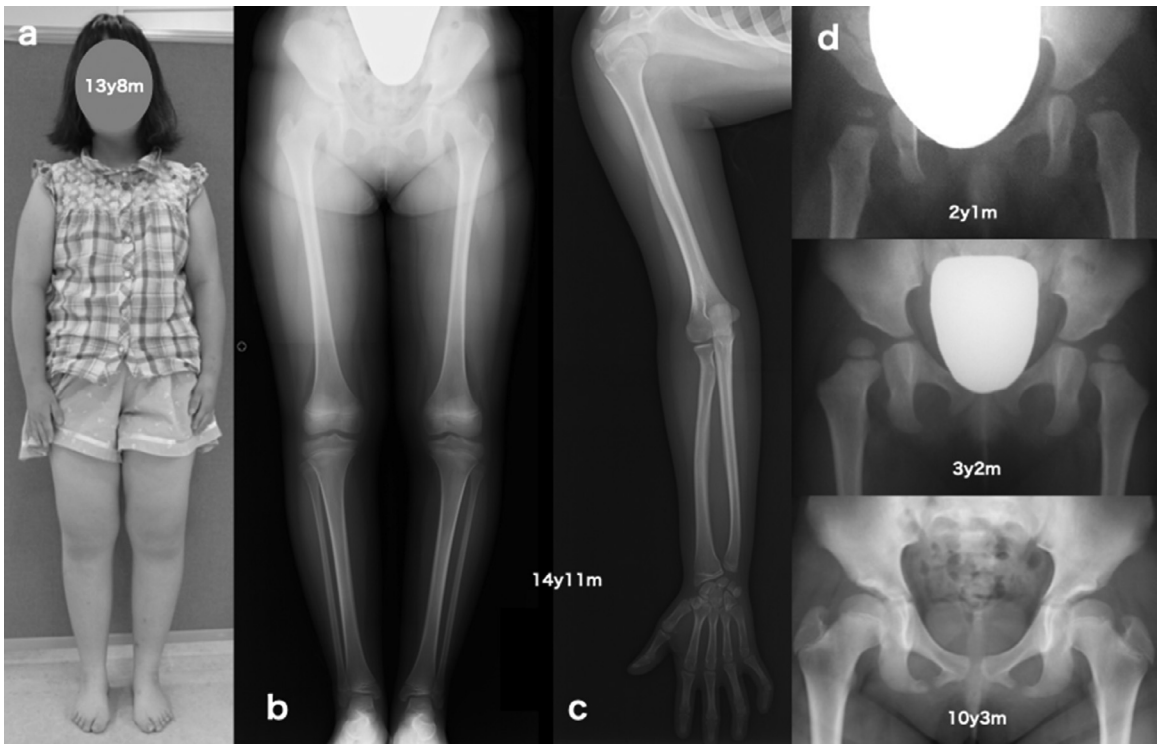

Fig. 2 – A full-length portrait and other radiological features of the patient. (a) Photograph of the whole body while standing. (b) Lower legs showed mild bow legs. (c) Right arm radiograph showed bowed radius and ulna. The ulna was shorter, which caused distal radio-ulnar deformity. (d) Both hips remained dysplastic from childhood to adolescence.

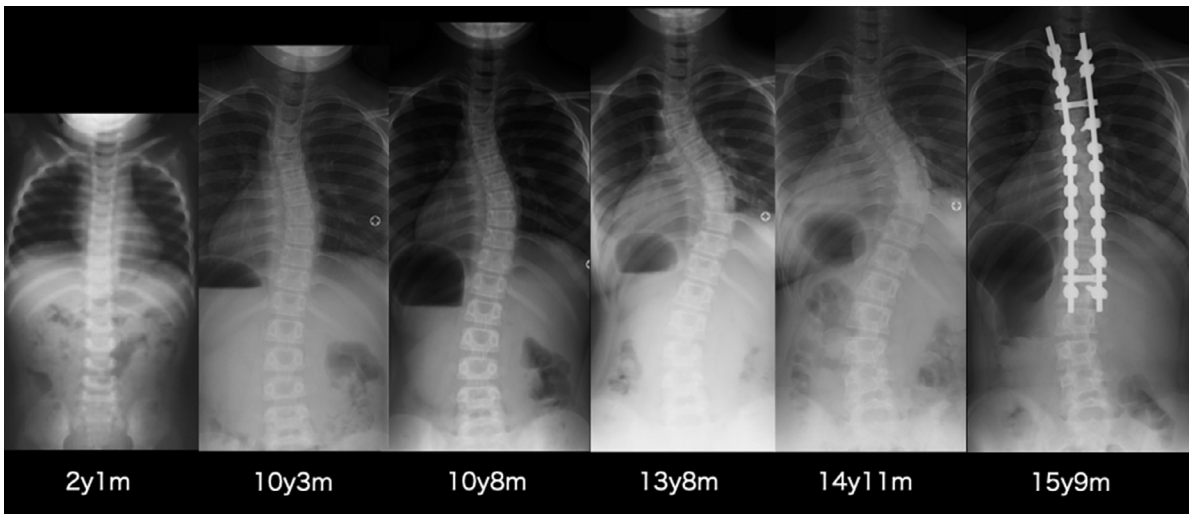

Fig. 3 – Progress of scoliosis depicted on the radiograph. Scoliosis developed in her adolescence and was surgically treated with posterior spinal fusion.

Discussion

Tsukahara-Azuno-Kaiji syndrome was first reported by Tsukahara, Azuno, and Kaiji in 1989 [1]. The second patient was reported by Utine et al. in 2010 [2]. Although they declared that this is a rare syndrome, no additional patients were reported in the following decade. To the best of my knowledge, this is the third case report on this syndrome.

The patient first visited the author's center when she was 5 months old. Finally, she was diagnosed with Tsukahara-Azuno-Kaiji syndrome at age 15 years and 6 months. The author was able to reach this diagnose through a simple web search. During these years, the amount of information on the

internet has increased dramatically, and even general clinical practitioners are now able to obtain proper knowledge of such rare diseases.

BDA1 is the most pathognomonic finding, and short stature, scoliosis, microcephaly, intellectual disability, ptosis, and mild hearing disability appear peculiar to this syndrome. Because this combination of features is very characteristic, the diagnosis is easy if clinicians know about this syndrome. Most of the features are radiological findings, and clinicians might be able to reach a diagnosis even using such features alone. As these symptoms do not cause fatal or severe dysfunctions, many patients with occult symptoms might be regarded as having simple psychomotor developmental delay or a simple BDA1 and might be neglected without diagnosis of Tsukahara-Azuno-Kaiji syndrome.

During the 2000s, several genetic mutations were identified, and currently 4 genetic subtypes of BDA1 are known. The mutations were found in the *Indian hedgehog (BDA1)* [4,5], *chromosome 5 (BDA1B)* [6], *GDF5 gene (BDA1C)* [7,8], and *BMP receptor type-1B (BMPR1B) gene (BDA1D)* [9]. Given its rarity, the relationship between Tsukahara syndrome and these genetic abnormalities is unknown. Unfortunately, the parents of the patient declined further examination of their daughter, so detailed genetic features were not investigated.

Despite reports of only 3 patients with this syndrome, a few common features can be identified. The disease occurred sporadically in all patients, and all of them were female.

As the number of patients diagnosed with this syndrome will increase, more data regarding their genetic information will become available, and the true nature of this syndrome will be gradually revealed.

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