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CONGENITAL LYMPHATIC DYSPLASIA IN KABUKI SYNDROME: FIRST REPORT OF AN UNUSUAL ASSOCIATION

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ABSTRACT

Kabuki syndrome was first described in Japan in 1981 as a rare disorder of unknown cause. Its main features include characteristic facies, postnatal growth retardation, and mental delay. To date, there is no molecular marker for Kabuki syndrome, which is considered genetically heterogeneous and still is a clinically-based diagnosis. Here we describe the first case of a patient affected by Kabuki syndrome associated with lymphatic dysplasia. We suggest accurate evaluation of all Kabuki patients as early as possible in order to diagnose lymphedema or other clinical manifestations of lymphatic system involvement. Early identification of lymphatic system maldevelopment provides the best chance for reducing the risk of developing progressive lymphedema with associated tissue changes (fibrosis, sclerosis, and fat deposition).

Keywords: lymphedema, Kabuki syndrome, Niikama-Kuroki syndrome, lymphscintigraphy, congenital lymphatic disorders

Kabuki syndrome is also known as Kabuki "make-up" syndrome or Niikawa-Kuroki syndrome (OMIM #147920). It was first described in Japan in 1981 as a rare disorder of unknown cause with characteristic facies, postnatal growth retardation, mental retardation and other anomalies (1,2). Prevalence of the syndrome is estimated to be at least 1 per 32,000, and no molecular cause has yet been determined (3,4).

The term "Kabuki" stems from the typical facial appearance of affected patients which resembles the make-up of actors of the traditional Japanese Kabuki theater. The main phenotypic features were described by Niikawa et al in 1988 (3) and include typical face presenting eversion of the lower lateral eyelids with arched eyebrows, depressed nasal tip, and prominent ears, brachydactyly, spinal deformities, fingertip abnormalities, mild to moderate mental retardation, and postnatal growth deficiency. To date, no molecular marker of Kabuki syndrome has been identified, thus the diagnosis is linked to accurate clinical observation and phenotyping.

The number of syndromic disorders in which congenital lymphatic dysplasia has been described is continuously increasing. Here we describe the case of a male patient affected by Kabuki syndrome associated with previously unreported lymphatic dysplasia.

CASE REPORT

The patient is a nine-year-old boy *(Fig. 1)* with developmental delay and mild growth retardation. His antenatal history and family history were not informative. He was born at term by natural vaginal delivery without asphyxia. Birth weight, height, and head

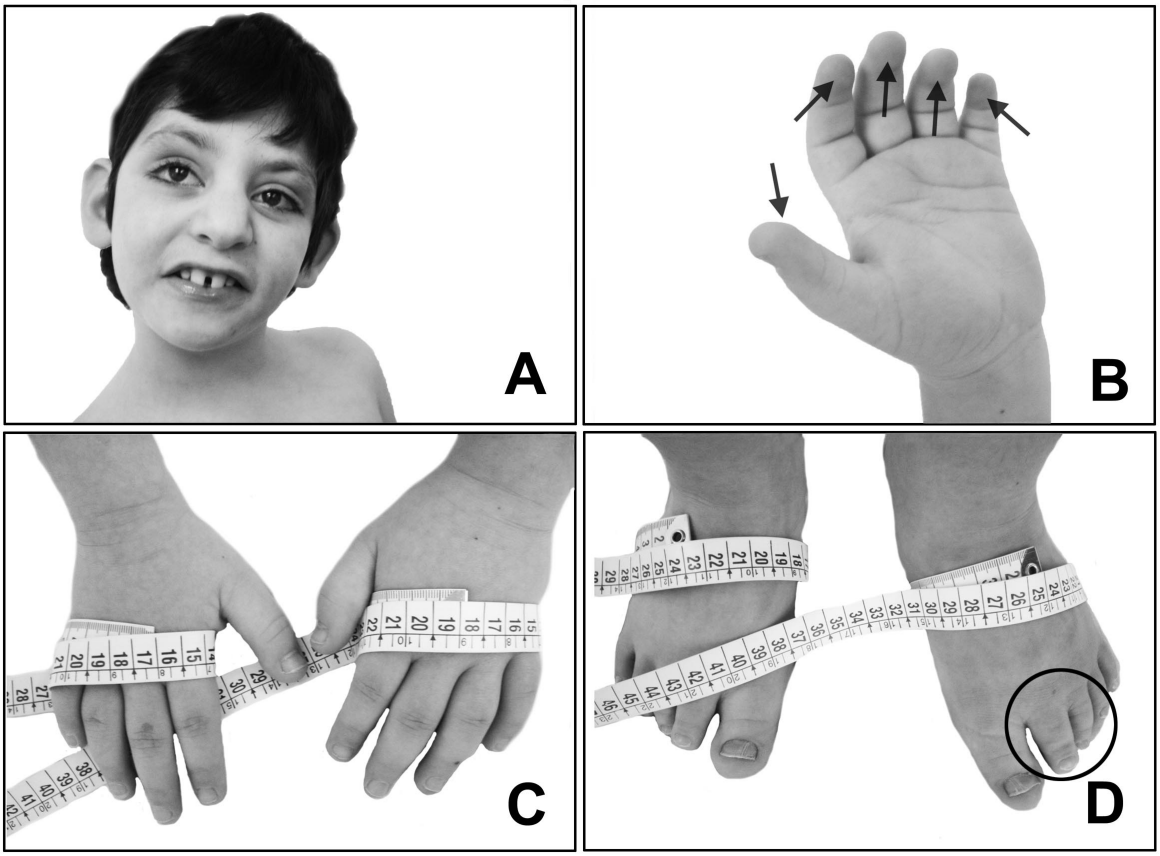

Fig. 1. Panel A. The patient at 8 years of age. Characteristic facial features of Kabuki syndrome. Note the long palpebral fissures, eversion of the lower eyelids, arched eyebrows, depressed nasal tip and prominent earlobes. Panel B. Arrows show typical fetal finger pads. Panels C and D. Swelling of the left hand (panel C) and swelling of the feet (panel D), both compatible with congenital lymphedema. Syndactyly of the second and third toes (panel D; open circle).

circumference were normal. He was referred to our Department at the age of two years because of growth retardation, multicystic right kidney, and dilatation of the left renal pelvis.

When we first saw him, his face had peculiar characteristics including long palpebral fissures, eversion of the lower eyelids, arched eyebrows, depressed nasal tip and prominent earlobes, which gave him facial features resembling a Kabuki actor. He also had other dysmorphic features including brachydactyly, prominent fetal finger pads, and syndactyly of the second and third toes. He had mild developmental delay: head control, walking without help and speaking meaningful words started at 8, 16 and 14 months of age, respectively.

Ultrasound kidney evaluation demonstrated the presence of a severely hypoplastic, multicystic right kidney and confirmed left renal pelvic dilatation. No other significant findings were observed by heart and abdominal ultrasound examinations, ECG and EEG studies, and auditory brainstem response evaluation. Karyotype was 46,XY (750 band-level resolution).

The patient remained stable at follow-up, showing non-progressive developmental delay and regular growth. At the age of eight years, he first presented with lymphedema of the right foot and hand. Lymphedema slowly

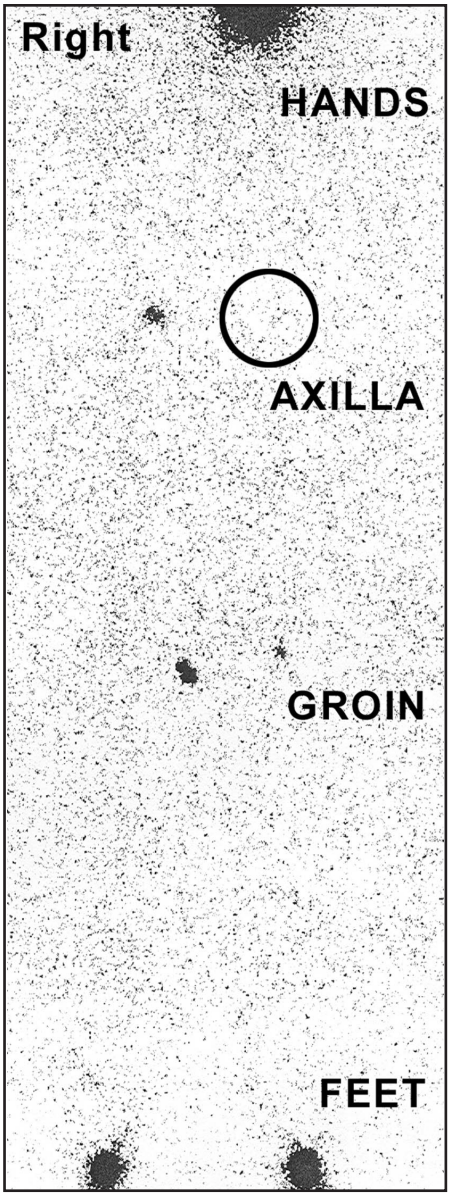

Fig. 2. Lymphscintigraphic study. The exam was performed at the onset of clinically evident lymphedema, when the patient was 8 years old. The patient was imaged with hands above the head and the injection sites for the hands together (top) and feet (bottom) can be seen in the image. Note the presence of hypoplasia of lymphatic vessels in both lower limbs and right arm with no evident lymphatic channels identified and small accumulation of tracer in regional nodes. Aplasia of the left arm lymphatic system is seen with lack of visualization of lymphatic vessels or nodes in the left axilla (open circle).

progressed despite treatment with bandaging and was followed by the onset of lymphedema in the left foot. Lymphscintigraphy was performed according to a previously reported protocol (5) at onset of lymphedema. The images revealed hypoplasia of the lymphatic vessels in both lower limbs and right arm, agenesis of the lymphatic vessels in the left arm, and no signs of dermal back-flow *(Fig. 2)*.

DISCUSSION

Kabuki syndrome is a rare congenital mental retardation-malformation syndrome affecting multiple organs. Kabuki syndrome has been associated with various chromosomal alterations including: pericentric inversion of the Y chromosome, a ring chromosome X or Y, a 45,X karyotype, interstitial duplication of 1p13.1p22.1, paracentric inversion of the short arm of chromosome 4, partial monosomy 6q and/or partial trisomy 12q, balanced translocation between 15q and 17q, pseudodicentric chromosome 13, 3.5 Mb duplication at 8p23.1p and 20p12.1 microdeletion (6), and, more recently, a mutation in the MLL2 gene (7). Nonetheless, the diagnosis of Kabuki syndrome still remains only clinical.

Adam and Hudgins described the diagnostic criteria: long palpebral fissures with eversion of the lateral portion of the lower lids, broad arched eyebrows with lateral sparseness, short columella with depressed nasal tip, prominent or cupped ears, developmental delay and mental retardation (8). These authors reviewed and reported all anomalies and disorders reported to be associated with Kabuki syndrome, including cardiac malformations, genitourinary anomalies, gastrointestinal defects, liver disease, endocrinopathies, immunodeficiency, and susceptibility to autoimmune diseases. However, they did not include any reference to congenital lymphatic dysplasia in their paper. They did describe the presence of unusual dermatoglyphic patterns and that the vast majority of patients also were found to have persistent fingertip pads, which are

considered a clear clue to the diagnosis (1-3,9,10) and suggest a correlation with the occurrence of prenatal disorders of the lymphatic system (11).

To our knowledge, this is the first report of the association between Kabuki syndrome and congenital lymphatic dysplasia. Although to date there are no reports of such an association, we hypothesize that the well-known presence of persistent fingerpads among the cardinal features of Kabuki syndrome might suggest a more extensive involvement of the lymphatic system. Primary lymphatic dysplasia is a congenital maldevelopment which interferes with the function of the lymphatic system and often causes effusion or reflux of chyle or lymph into the limbs or into the pleural, pericardial or peritoneal cavities. This dysplasia may be present at birth or early in childhood and early diagnosis is important in order to prevent or minimize the rapid evolution of lymphedema and associated visceral chylous effusions.

We have recently demonstrated (12) that lymphscintigraphy evaluation may be "preclinical," meaning that this technique can demonstrate the presence of lymphatic system maldevelopment before its clinical onset. Accordingly, we suggest accurate evaluation of all Kabuki patients as early as possible in order to diagnose lymphedema or other clinical manifestations of lymphatic system involvement in an effort to obtain improved follow-up and control. Clinical disorders that are characterized by functional lymphatic insufficiency currently lack a cure and reducing the progression of lymphatic impairment is a main goal (13). Lymphscintigraphy should be considered for all patients with congenital malformation syndromes, such as Kabuki syndrome, who present minimal signs of lymphatic system disorders and therefore, must be considered at risk for developing lymphedema and associated tissue changes of fibrosis, sclerosis, and fat deposition.

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