What Syndrome Is This?

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CASE REPORT

A 4-year old boy, the only son of healthy, nonconsanguineous parents without a significant family history, was referred to our clinic. Pregnancy had been complicated by missed abortion and decrease in fetal movements, and he was born at term with prolonged labor, resulting in perinatal distress. At birth, his weight was 4 kg (75th centile), height 51 cm (50th centile), head circumference 35 cm (50th centile), and Apgar score was 5 at first minute and 8 at fifth minute; he had general hypotonia, prolonged icterus, and feeding difficulties. Laboratory and instrumental examinations (standard karyotype and FRAXA, nervous system imaging, metabolic and hormonal studies, TORCH, total body radiograph, ophthalmologic examination) performed successively, within the first year of life, gave no remarkable results. The psychomotor development of the patient was delayed: he was able to walk unsupported at about 15 months of age, and pronounced his first monosyllabes at 24 months. He was very susceptible to respiratory infections.

On examination, he was 107 cm tall (50th centile), his weight 22 kg (90th centile), and OFC 53 cm (90th centile). He presented with an expressionless face, low-cut hairline, frontal bossing, arched and laterally sparse eyebrows, long palpebral fissures with lower palpebral eversion, epicanthus, telecanthus (abnormally increased distance between medial canthi), a short, flat nose with anteversion of the tip and short philtrum, large mouth with thick lips (lower lip was also everted), high-arched palate, thick tongue, teeth malocclusion and micrognatia, and large protuberant low-set ears with a thick helix (Fig. 1). Abnormalities were not restricted to the craniofacial area; they also involved the upper limbs (brachydactyly, prominence of fingertip pads, clinodactyly of fifth finger bilaterally, abnormal palmar creases) (Fig. 2) and lower limbs (genu valgum, shortness of great toes, cutaneous syndactyly of second and third toes of both feet). He also had unilateral right cryptorchidism.

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Kabuki make-up syndrome (Niikawa-Kuroki syndrome).

DISCUSSION

This rare syndrome (about 350 patients reported in the literature) was first described in 1981 by two independent groups—Niikawa et al (1) and Kuroki et al (2). The syndrome is comprised of multiple congenital anomalies and mental retardation of unknown cause. The term “Kabuki make-up syndrome” was given because of the most striking feature of the face of patients, the eversion of the lower lateral eyelid, which resembles the make-up of the actors of Kabuki, a traditional form of Japanese theater.

According to Niikawa et al (3), cardinal manifestations of the syndrome can be divided into five categories: craniofacial, skeletal and dermatoglyphic abnormalities with mental retardation and short stature. Only craniofacial abnormalities are always present; the other features are helpful for making the diagnosis, but are not a prerequisite.

In 2003 Matsumoto and Niikawa reviewed 13 different series of patients (251 patients in total) (4), compiling...
a complete list of all known clinical features of the syndrome (summarized in Table 1). In addition to the aforementioned cardinal manifestations, other clinical signs reported in patients with Kabuki make-up syndrome are visceral abnormalities (ventricular or atrial septal defect, coarctation of the aorta, patent ductus arteriosus, transposition of great vessels, renal/urinary tract malformations, biliary atresia, diaphragmatic hernia, anorectal anomalies) and a higher susceptibility to infections such as otitis media, upper respiratory tract infections, and pneumonia; in single patients, severe immunodeficiency or autoimmune diseases (autoimmune hemolytic anemia and polycytemia, chronic idiopathic trombocytopenia, acquired hypogammaglobulinemia with anti-IgA antibodies) were demonstrated (4–8). Some authors also observed the presence of abnormal hair (trichorrhexis nodosa, caliber irregularities, twisting of the hairshaft, “scanty scalp hair”) and abnormal nails (short and fragile nails); these abnormalities, together with commonly described tooth abnormalities, suggest an ectodermal dysplasia involvement in Kabuki syndrome (9–11).

Diagnosis is exclusively based on clinical features, as no specific laboratory, histopathologic, or other investigative tools have been identified that might help with the diagnosis.

Differential diagnoses include Turner syndrome, Noonan syndrome, and Hardikar syndrome (12). Patients with Turner syndrome have a high incidence of cardiac defects, and those with a very small ring X-chromosome may present with a close facial resemblance to Kabuki syndrome, because of long palpebral fissures; however, these patients can be identified because they lack other facial features of Kabuki syndrome including everted lower lateral eyelids, arched eyebrows, prominent ears, and fetal pads. In Noonan syndrome, patients have a webbed neck, low posterior hair line, low-set ears, ptosis of the eyelids, and widely spaced nipples that can mimic some infrequent clinical signs of Kabuki syndrome; however, long palpebral fissures and fetal pads are not present in Noonan syndrome. Some facial similarity can also be noted between Kabuki syndrome and Hardikar syndrome, characterized by long palpebral fissures, obstructive liver disease, and retinopathy.

Figure 1. Facial appearance.

Figure 2. Short finger (5th), clinodactyly (5th), and dermatoglyphic abnormalities.
The genetic defect responsible for Kabuki syndrome is still unknown. Milunsky et al (13) recently reported chromosome 8p22-8p23.1 duplication in six patients, but Miyake et al (14) were unable to reproduce their results, although using the same technique, in another 28 patients. Reports in the literature document some instances of autosomal dominant inheritance (11), and hypotheses were made about insertional balanced translocation and small ring X-chromosome (4). However, as the vast majority of patients have sporadic disease, with new mutations, and the disease has a wide spectrum of clinical manifestations, it is likely that Kabuki syndrome is caused by microdeletions involving many contiguous genes (“contiguous gene syndrome”) (4).

The natural history and prognosis of Kabuki syndrome are good, although the quality of life and survival can be significantly different among patients. The main complications are infectious, cardiovascular, hepatic or renal diseases that can become critical when combined with the frequent immunodeficiency. Mental retardation is seldom severe. According to Matsumoto and Niikawa (4), woman subjects with normal or mildly reduced intelligence are fertile, and literature reports state that most women affected by the syndrome have regular menstruation. The issue of men fertility is unknown, although at least four fathers with facial characteristics of Kabuki syndrome have been reported in the literature. The natural history of this syndrome is poorly studied because of the rarity of the condition and the lack of prolonged follow-up in the majority of patients (8,15); studies on a larger series of patients are needed.

No treatment is available; preventive and therapeutic interventions should be aimed at avoiding the frequent complications.

REFERENCES