Hypermobility in individuals with Kabuki syndrome: The effect of growth hormone treatment

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1 | INTRODUCTION

Kabuki syndrome (KS; OMIM 147920) is a multiple congenital malformation syndrome that was independently described by Kuroki, Suzuki, Chyo, Hata, and Matsui (1981) and Niikawa, Matsuura, Fukushima, Ohsawa, and Kajii (1981). Although there are no scientific reports on the overall incidence of KS, it has been reported across almost all ethnic groups and its prevalence outside Japan presumably approximates that seen in the Japanese population, that is, one in 32,000 (Adam, Hudgins, & Hannibal, 1993; Niikawa et al., 1988). Clinical features of KS include developmental delay or intellectual disability, hypotonia, postnatal growth retardation, presence of fetal fingertip pads, and characteristic facial features. These features include long palpebral fissures with eversion of the lateral portion of the lower eyelid; broad, arched eyebrows with lateral sparseness; short columella with depressed nasal tip; and large, prominent or cupped ears (Schrander-Stumpel, Spruyt, Defloor, & Schrander, 2005). In 2010, Ng et al. performed whole exome sequencing in 10 cases clinically diagnosed with KS and discovered the cause as mutations in the KMT2D gene (formerly MLL2; MIM# 602113; NM 003482.3; Makrythanasis et al., 2013; Ng et al., 2010). Since then, KMT2D mutations have been identified in approximately 56–70% of the clinically diagnosed individuals (Bogershausen et al., 2016; Paulussen et al., 2011). In the same period, a second gene was determined to be responsible for a subgroup of KS patients: KDM6A (formerly UTX; MIM# 300128; NM 021140.3), a partner of KMT2D in its pathway (Lederer et al., 2012). This led to the definition of two subtypes of KS: KMT2D-associated, autosomal-dominant KS type 1 (KS1; OMIM 147920); and KDM6A-associated, X-linked-dominant KS type 2. Generalized joint hypermobility is one feature of KS, but its exact incidence and pattern is not well described in the literature. As part of our prospective study on the metabolic and growth effect of GH treatment, we assessed children from our Dutch Kabuki cohort who were eligible for growth hormone therapy. We assessed severity and pattern of joint hypermobility, both before and after 24 months of growth hormone replacement therapy. The prevalence of hypermobility was 31% in boys and 14% in girls using the Beighton score and 69% in boys and 57% in girls using the Bulbena score. This varies from the general population where girls are more affected. After 2 years of growth hormone treatment, there was a statistically significant decrease in the presence of joint hypermobility to 6% using the Bulbena score and none with respect to the Beighton score. We hypothesized that this result suggests a direct effect of growth hormone on connective tissue in patients with KS.

KEYWORDS

growth hormone treatment, joint hypermobility, Kabuki syndrome, KDM6A, KMT2D
KS) is mentioned; however, this has never been formerly assessed within a KS population (Bogershausen & Wollnik, 2013). Therefore, we decided to assess hypermobility in children with KS and to evaluate whether growth hormone treatment affects hypermobility in patients with a proven mutation causing KS by re-assessing hypermobility scores after 12 and 24 months of growth hormone replacement therapy. This research is part of our Dutch KS Center prospective study on the metabolic and growth effect of GH treatment in children with KS (Schott, Gerver, & Stumpel, 2017).

2 | METHODS

This study was performed as an open-label, prospective, nonrandomized study of KS children (trial registration: NTR4722) at the Maastricht University Medical Centre Maastricht, The Netherlands. Participants were recruited between 2012 and 2014. In total 27 KS children (13 males and 14 females) were included. Their mean age was 8 years (2–18 yr). Subjects with previous growth hormone therapy were excluded. Twenty-four of the KS individuals had a KMT2D mutation and three had a KDM6A mutation. The Medical Ethics Committee of the Maastricht University Medical Centre provided ethical approval of the study. Informed consent was obtained from the subjects’ parents before the start of the study.

Of the 27 subjects, 18 KS children (9 females and 9 males) were also included in a growth hormone study. Not all 27 subjects could receive growth hormone treatment because of the influence of pubertal hormones, as has been described in earlier publications on this study (Schott, Gerver, & Stumpel, 2016). Subjects with diabetes mellitus, an extremely low caloric intake, a previous or active malignancy, and children with signs of puberty were excluded. Biosynthetic human GH (Genotropin, Pfizer, New York, NY) was given subcutaneously once daily at bedtime. The average dose was 1 mg/m²/day GH (equivalent to 35 μg/kg/day) for 12 months. The initial dose of GH was altered based on IGF-I levels and/or growth hormone response described previously (Schott et al., 2016; Schott et al., 2017). IGF1 levels?

Generalized joint laxity was assessed using the modified Beighton 9-point scoring system by trained clinicians (MK and JS) in the research clinic for children with KS. As described by Junge et al., each joint was assessed separately (Junge, Jespersen, Wedderkopp, & Juul-Kristensen, 2013). With a score of 7 or more a child was considered as having generalized hypermobility. Because the Beighton scoring system only includes a limited number of joints, the Bulbena et al. scoring criteria was also employed to assess several joints separately, although this score has not been validated in large groups of children. Generalized hypermobility of the joints is present when a score of five is obtained in females and four in males (Bulbena et al., 1992).

Descriptive statistics are shown as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to test for normal distribution. Intragroup comparisons were made with the paired Student’s t test. For intergroup comparisons, the independent Student’s t test was employed. All statistical analyses were performed using the software SPSS version 22 for Mac (SPSS Inc., Chicago, IL). A p-value of <.05 was considered significant.

3 | RESULTS

Twenty-seven KS children were assessed using both scores, before starting growth hormone replacement therapy. They were between ages 2 and 18 years old at the time of the first assessment and their mean age was 8.0 years (Table 1). Twenty-five children were Caucasian, one subject was Asian and another one was from Northern Africa. The parents of 21 (78%) of them believed their child was hypermobile, based on their own observations and information they read in literature. Using the Beighton score the prevalence of hypermobility was 31% in boys and 14% in girls. For the Bulbena score it was 69% in boys and 57% in girls, respectively. The mean age for a positive score in the Beighton group was 7.7 ± 4.6 years and 7.3 ± 4.3 years in the Bulbena group, respectively. The mean age for a negative score in the Beighton group was 8.0 ± 3.9 years and the Bulbena group 9.1 ± 3.2 years. There was no statistically significant difference between boys and girls. Joints most often affected included the hip, knee, and fifth finger (Figure 1). No significant gender differences in affected joint pattern of joints were discovered.

Three of the 27 children had a KDM6A mutation and had the same hypermobility as the KMT2D subjects. Only one of the KS children had a patellar luxation in here previous history and was not considered hypermobile using both scores. The children with other orthopedic anomalies in their history, such as hip dislocations, were all considered to be hypermobile using both scores (Table 2).

Eighteen children (67%, 9 males and 9 females) were also assessed in a growth hormone study. Age, height, and BMI between the males and females were not significantly different. At the start of GH treatment, the mean age was 6.9 ± 2.1 years (ranging from 3.8 to 10.1 years, median 6.95). Four KS individuals were GH deficient, but this had no influences on hypermobility. Baseline characteristics are shown in Table 3. Serum IGF-I levels were measured at baseline, and at 12 months of GH therapy. At the start, the IGF-I SDS had a mean of −0.70 ± 1.07, which increased significant after 12 months of GH

### TABLE 1 Baseline characteristics of all 27 KS subjects, including hypermobility scores

|               | Male     | Female   | All      |
|---------------|----------|----------|----------|
| Sex           | 13       | 14       | 27       |
| Age (mean ± SDS) | 8.6 ± 4.3 | 7.4 ± 3.7 | 8.0 ± 3.9 |
| Mutation      | KMT2D    | 12       | 12       | 24       |
|               | KDM6A    | 1        | 2        | 3        |
| Positive test | Beighton (score) | 4        | 2        | 6        |
| Bulbena (score) | 9        | 8        | 17       |
| Beighton (mean age ± SDS) | 9.2 ± 5.1 | 4.8 ± 1.6 | 7.7 ± 4.6 |
| Bulbena (mean age ± SDS) | 8.9 ± 5.1 | 5.6 ± 2.4 | 7.3 ± 4.3 |
| Beighton score | (Mean ± SDS) | 4.7 ± 2.2 | 4.2 ± 2.4 | 4.4 ± 2.3 |
| Bulbena score | (Mean ± SDS) | 5.8 ± 2.9 | 5.2 ± 2.0 | 5.5 ± 2.5 |

SDS = standard deviation score.
The height also significantly increased from $-2.40$ to $-1.69$ (+0.7) SDS for the entire study group after 1 year of treatment.

Both Beighton and Bulbena assessments were performed at start and after 12 and 24 months of GH therapy. Details of the hypermobility of all 18 subjects at these three points in time are given in Table 4. Only in four individuals both scores were not assessed after 24 months of GH treatment and are not included in Table 4. After 2 years of growth hormone replacement therapy there was a statistically significant decrease in the presence of joint hypermobility from 61% to 6% using the Bulbena score for assessment ($p = .03$, $p$-value <.05). Using the Beighton score, there was a decrease from 33% to 0% ($p = .01$). This effect of GH treatment on the hypermobility was equal in males and females. No differences were observed in mutation, GH deficiency or catch-up growth.

**DISCUSSION**

This is the first article to specifically describe hypermobility in children with genetically confirmed KS. As reported previously generalized hypermobility is one of the key features of KS. This study also confirms the presence of hypermobility in these children. However, with hips and knees most affected, our work found the pattern less generalized than previously thought. Furthermore, we demonstrate that growth hormone treatment has a positive effect on this hypermobility.

Joint hypermobility means the ability to move joints beyond the normal range of movement without pain. It can occur in only one joint or in almost all joints of an individual with general hypermobility. Joint hypermobility is a normal variability in the population, usually present as an autosomal dominant trait in families. However, it can also indicate an underlying connective tissue disease. Then, it is usually accompanied by weakness and/or abnormal stretching of connective tissue in skin and vascular wall.

Joint hypermobility is frequently described as a feature of monogenic syndromes or chromosomal anomalies without being part of an obvious connective tissue disease. Although no data exist, it is our

| Condition                          | Percentage (% of total) |
|------------------------------------|-------------------------|
| Hip dysplasia                      | 19%                     |
| Patella dislocation                | 4%                      |
| Subluxation other joints           | 7%                      |
| Scoliosis                          | 0%                      |
| Abnormal scarring                  | 4%                      |
| Abnormal stretching of skin        | 4%                      |
| Hematomas                          | 7%                      |

**TABLE 3** Baseline data (mean ± SDS) and the auxological data after one-year of GH treatment of all 18 subjects

| GH treatment                  | Pretreatment | One-year treatment |
|------------------------------|--------------|--------------------|
| Chronological age            | 6.86 ± 2.07  | 7.97 ± 2.13        |
| Bone age                     | 5.90 ± 2.14  | 7.28 ± 2.37        |
| Height SDS                   | −2.40 ± 1.88 | −1.69 ± 1.94*      |
| Height velocity (cm/y)       | 6.55 ± 2.66  | 9.66 ± 2.04*       |
| Height velocity SDS          | 0.29 ± 2.43  | 2.80 ± 1.56*       |
| Parent-adjusted height SDS   | −2.07 ± 1.66 | −1.35 ± 1.61*      |
| Weight SDS                   | −1.34 ± 2.88 | −1.16 ± 2.62       |
| BMI SDS                      | 0.56 ± 1.79  | 0.19 ± 1.41        |
| IGF-I SDS                    | −0.70 ± 1.07 | 1.41 ± 0.91*       |

SDS = standard deviation score.

*Statistically significant ($p < .05$) relative to baseline.

**FIGURE 1** Pattern of hypermobility of separate joints (Bulbena score). Percentage of children with hypermobility of these joints, before growth hormone replacement therapy.
experience that in those cases the pattern of hypermobility is more variable, with often only a few joints affected. Sometimes surgery is needed, but this frequently leads to unsatisfactory results, as has been described in other children with connective tissue disorders (Klaassens et al., 2012).

In the literature, hypermobility is described in up to 75% of individuals with KS. There is no specific literature on the etiology of joint hypermobility in KS, although Philip et al. suggested that KS might be a connective tissue disorder. However, no other research supports this assertion. Indeed, given the function of the genes responsible for KS, that finding is suspect (Philip et al., 1992). A high prevalence of congenital dislocation of the hip was already reported in the first publications by Kuroki et al. (1981) and Nakawa et al. (1981) (Schrander-Stumpel et al., 2005). Philip et al. reported on 16 patients outside of Japan. Of these, 10 patients had hypermobile joints including hip dislocation, a finding not previously reported in the Japanese literature (Philip et al., 1992). The researchers suggested the frequency of hip dislocation in the Japanese patients might reflect an unrecognized general joint laxity. Schrander-Stumpel et al. also reported joint hyperlaxity in 90% of the individuals from the Dutch Kabuki Center, none of whom are included in the current study. Hip dislocation occurred in 28% of their cohort (Schrander-Stumpel et al., 2005). Kurosawa et al. reported three patients with recurrent dislocation of the patella (Kurosawa et al., 2002). All three patients had generalized ligamentous laxity. Kawame et al. reported patients with patellar dislocation, congenital hip dysplasia and recurrent shoulder dislocations (Kawame, Hannibal, Hudgins, & Pagon, 1999). One patient in the literature was reported with cutis laxa as well as hyperextensible joints (Vaccaro et al., 2005). We did not find patients with cutis laxa in our cohort nor is it mentioned as a Kabuki feature in any of the other studies as a phenotypical description of the syndrome.

KS is one of the syndromes in which hypermobility is considered a main feature, although the exact prevalence remains unknown. Therefore, we assessed all children eligible for the study from our cohort at the Dutch Kabuki Expertise center for the effects of growth hormone (Schott et al., 2017). Within this group of 27 children with KS between the ages of 2 and 18 years old, we found that 14–69% were considered to have general hypermobility using both the Beighton and Bulbena scoring systems. There was no difference between boys and girls. This is in contrast to the general population in which the prevalence of general hypermobility is considered to be higher in girls (Junge et al., 2013).

Both the Beighton and Bulbena scores were used for assessment of hypermobility and both have been validated for use in children, although the Bulbena score has not been validated in large cohorts (Junge et al., 2013; Smits-Engelsman, Klerks, & Kirby, 2011). In our experience, the Beighton score is less useful in children with syndromal anomalies since it only includes a limited number of joints, notably not the ones most often affected in these populations. This applies both to our cohort of Kabuki patients for whom the hips are most often affected and in children who do not fulfill the criteria for general hypermobility from both scoring systems. This localized hypermobility also accounts for the higher percentage of hypermobility found with the Bulbena score compared to the Beighton score, given the fact that the Bulbena score includes those joints most often affected in KS (e.g., hip, knee and ankle, all not included in the Beighton score). All studies performed with these scores were focused on healthy children. Therefore, it is unclear whether these scoring systems apply to a population of children with an underlying genetic anomaly not directly affecting connective tissue but in whom the hypermobility might also be caused, at least in part, by a neuromuscular component.

In addition to a description of incidence of hypermobility we also assessed hypermobility after 1–2 years of growth hormone replacement therapy, since it is known that growth hormone can have a number of positive effects on growth and development. Several syndromes (e.g., Turner syndrome, Prader Willi Syndrome) without a real growth hormone deficiency have proven benefited from growth hormone treatment at supraphysiological doses by obtaining a higher final height than expected (Reh & Geffner, 2010). However, more beneficial effects than those on final height involve changes in body composition and the increase in muscle mass (van Mil et al., 2001; Festen et al., 2008). We hypothesize that children with KS present more negative effects of hypermobility on their motor development because of the fact that their muscle mass is also low and they have hypotonia, which may be severe. Indeed, in all children that could be assessed after 2 years of treatment, hypermobility decreased and even disappearing in most cases. Furthermore, nearly all parents spontaneously reported significant improvements in motor skills. Given our study’s design, it was not possible to pinpoint the mechanism exactly, but it seems likely that growth hormone might have a direct effect on connective tissue. It is known that an excess of growth hormone can lead to stiffness and joint pain, as seen in patients with acromegalic arthropathy (Denko & Boja, 2001). It is also known that joint stiffness is considered an adverse event in growth hormone treatment. However, in patients with hypermobility this joint stiffness might be considered a desirable effect. A possible mechanism by which growth hormone induces joint stiffness is the induction of decorin, a structural protein in the skeletal muscle extracellular matrix that regulates genes for muscle growth and repair. Through this mechanism, growth hormone treatment stimulates muscle and tendon collagen synthesis (Bahl, Stone, McLean, Ho, & Birzniec, 2018). Further research on the exact mechanism by which growth hormone replacement therapy improves hypermobility in KS is needed.

5 | CONCLUSION

Hypermobility is indeed a feature of KS as described in the literature. We are the first to formerly assess a Kabuki cohort on this feature and its distribution. Growth hormone replacement therapy has many beneficial effects on children with KS, including a significant improvement in joint hypermobility, but the exact mechanism for this improvement is not yet known.

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research. This project was part of our prospective study on the metabolic and growth effect of GH treatment, which has been approved by the Medical Ethics Committee of the Maastricht University Medical Center and the Clinical Trial Center Maastricht.

CONFLICT OF INTEREST
The author reports no conflicts of interest in this work.

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