Body proportions in children with Kabuki syndrome

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Body Proportions in Children with Kabuki Syndrome

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Facial characteristics, short stature, and skeletal anomalies have been described for the clinical diagnosis of Kabuki Syndrome (KS) in children. However, no studies have investigated body proportions in KS. Knowledge of body proportions in KS may contribute to better insight into the growth pattern and characterization of this genetic disorder. Therefore we compared body proportions of children with KS to normally proportioned controls to investigate if atypical body proportions are part of this genetic disorder. This study was designed and conducted within the setting of the Maastricht University Medical Centre (MUMC+), the official Dutch expert center for Kabuki syndrome. We conducted a cross-sectional study in 32 children (11 children with KS and 21 controls). Body proportions were determined by means of photogrammetric anthropometry, measurements based on digital photography. Body proportions, quantified as body ratios, differ significantly in children with KS from normally proportioned children. Children with KS have larger heads and longer arms proportional to their trunks and have been found to have longer upper arms proportional to their tibia length and feet. Based on deviations in body proportions it was shown possible to discern children with KS from normally proportioned controls. © 2015 Wiley Periodicals, Inc.

Key words: Kabuki syndrome; body proportions; photogrammetric anthropometry; children

INTRODUCTION

Children with Kabuki syndrome (KS) are characterized by a distinct facial appearance, mild to moderate intellectual disability, postnatal growth retardation, skeletal anomalies, and unusual dermatoglyphic patterns [Niikawa et al., 1981]. Two genes have shown to be mutated in patients with KS, 55–80% present mutations in the *MLL2/KMT2D* gene and in 9–14% the *KDM6A* gene is mutated [Ng et al., 2010; Lederer et al., 2012; Dentici et al., 2015].

The facial characteristics, which are used in the clinical diagnosis of KS, have been described extensively in recent literature, several studies also describe the presence of short stature and skeletal anomalies in KS [Niikawa et al., 1981; Wilson, 1998; Mhanni et al., 1999; Digilio et al., 2001; Shotelersuk et al., 2002; Schrand-

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Stumpel et al., 2005]. However, no studies have investigated body proportions in these children. Knowledge of body proportions in KS may contribute to better insight into the growth pattern and characterization of this genetic disorder. Therefore we performed a cross-sectional study to compare body proportions of children with KS to normally proportioned controls.

METHODS

This study was designed and conducted within the setting of the Maastricht University Medical Centre (MUMC+), the official Dutch expert center for Kabuki syndrome. We work in close collaboration with the Dutch Kabuki Network.

Study Groups

In total, 11 children, between 3 and 16 years old, visiting the expert center for Kabuki syndrome in the Maastricht University Medical Centre were included in this study. KS was confirmed in all participating children based on the presence of gene mutations in *MLL2/KMT2D*. No mutations in *KDM6A* were found. For the control group, 21 children between 2 and 14 years old, visiting the

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outpatient clinic of Endocrinology and Growth of the Maastricht University Medical Centre were included. These children were all growth hormone deficient and received adequate growth hormone therapy. These children were all proportioned normally according to the Dutch reference values [Gerver and de Bruin, 2011]. Before inclusion, all patients and/or their parents had given informed consent.

Measurements

In a previous study, we developed a new method for taking anthropometric measurements, using photogrammetric anthropometry. It was shown to be a fast, easy to use, validated method to take elaborate anthropometric measurements of the whole body, especially body proportions [Penders et al., 2015]. Collected data used in this cross-sectional study are digital photographs taken of the children in underwear. Photographs are taken in a frontal and lateral position and measurements on these photographs are performed using the photometry software *Paediatric Morphometrics* designed by our research group. Digital photographs were taken conform the photogrammetric method described previously [Penders et al., 2015]. Body proportions were determined according to the measurements of various anthropometric distances by selecting anatomical reference points in the photographs. These are the same reference points used in manual measurements [Gerver and de Bruin, 2011]. The measurements included: height (H), biacromial width (Biac), biiliacum width (Biil), upper arm length (UA), lower arm length (LA), hand length (HA), tibia length (Tibl), and foot length (FO). Additionally, head length (HI) was determined on the photograph as the height difference between the top of the head and the chin. Trunk length (Trl) was determined as the height difference between biacromial width and biiliacum width. Arm length (ARM) was

determined as the summation of upper arm length, lower arm length, and hand length.

Statistical Analysis

All data were exported to IBM SPSS Statistics for Windows version 20.0 for statistical analysis. Shapiro–Wilk tests were performed for all measurements to test for normality. Comparison of different groups was done using independent student *t*-test, Mann Whitney U test or Fisher's exact as appropriate.

RESULTS

Characteristics of the Study Participants

A total of 32 children were enrolled in this study (11 children and 21 controls). Both groups were comparable regarding age and gender. Significant differences between groups were seen in several proportional measurements. All characteristics are presented in Table I.

The eight ratios HI/H, Trl/H, HI/Trl, ARM/Trl, UA/Tibl, UA/FO, Tibl/H, and FO/Tibl show significant differences between children with KS and normally proportioned children. When presented for age, the ratios HI/Trl, ARM/Trl, UA/Tibl and UA/FO show distinct distribution differences. These distributions are presented in Figures 1–4 where the black dots represent the control group and the white dots represent the KS group.

DISCUSSION

To our best knowledge, this is the first report on body proportions in children with Kabuki syndrome. We used photogrammetric

TABLE I. Characteristics of the Study Participants

	Children with KS	Controls	P-value
N	11	21	
Gender m/v (%)	58/42	76/24	0.433
Age (range)	8.3 ± 3.4 [3.7–16.0]	10.2 ± 3.3 [2.6–14.8]	0.138
HI/H	0.20 ± 0.03	0.17 ± 0.02	<0.001
HI/Trl	0.82 ± 0.07	0.55 ± 0.06	<0.001
Biac/Biil	1.25 ± 0.12	1.22 ± 0.07	0.363
Biac/H	0.22 [0.20–0.23]	0.23 [0.22–0.23]	0.457
Biil/H	0.17 [0.16–0.20]	0.18 [0.18–0.19]	0.123
Trl/H	0.25 [0.23–0.26]	0.30 [0.29–0.32]	<0.001
ARM/H	0.43 [0.38–0.45]	0.42 [0.41–0.43]	0.289
ARM/Trl	1.76 [1.68–1.88]	1.35 [1.31–1.47]	<0.001
UA/LA	1.24 ± 0.16	1.21 ± 0.07	0.565
UA/Tibl	0.97 ± 0.06	0.76 ± 0.05	<0.001
UA/FO	1.30 ± 0.09	1.09 ± 0.09	<0.001
Tibl/H	0.19 ± 0.02	0.23 ± 0.01	<0.001
Tibl/Trl	0.80 [0.77–0.84]	0.77 [0.70–0.79]	0.051
FO/Tibl	0.75 ± 0.07	0.70 ± 0.05	0.027

H, height; HI, head length; Biac, biacromial width; Biil, biiliacum width; Trl, trunk length; UA, upper arm length; LA, lower arm length; HA, hand length; ARM, arm length; Tibl, tibia length; FO, foot length. Data presented as mean ± SD or as median [IQR].

FIG. 1. HI/Trl distribution for age; HI, head length; Trl, trunk length.

FIG. 3. UA/Tibl distribution for age UA, upper arm; Tibl, tibia length.

FIG. 2. ARM/Trl distribution for age ARM, arm length; Trl, trunk length.

FIG. 4. UA/FO distribution for age UA, upper arm; FO, foot.

anthropometry to estimate the body proportions of these children and compared the results to a reference group of normally proportioned children. We also used this method to determine if atypical body proportions are a characteristic feature in children with KS. The ratios HI/Trl, ARM/Trl, UA/Tibl, and UA/FO for age in children with KS clearly differentiate from the reference group.

These ratios show that children with KS have larger heads and longer arms proportional to their trunks compared to normally proportioned children. Additionally, children with KS have been found to have longer upper arms proportional to their tibia length and feet. These differences can be quantified as proportional cut-off values which are independent of age. In all children with KS a

HL/Trl ratio >0.71 was found, opposed to the reference group which showed a HL/Trl ratio <0.71 . Similar results were found for ARM/Trl (>1.63 for KS), UA/Tibl (>0.87 for KS) and UA/FO (>1.18 for KS). Based on these deviations in body proportions it was shown possible to discern children with KS from normally proportioned controls. Analysis of these body proportions can be done accurately with photogrammetric anthropometry, which is a fast, low-cost, and easy to perform method.

In other conditions where short stature and skeletal anomalies are present, such as idiopathic short stature (ISS), SHOX gene (short stature homeobox-containing gene) defects, and Turner syndrome (TS), more research has been done on body proportions. In an extensive study of Malaquias et al. abnormal body proportions were observed in 88% of the children with SHOX-defects, 48% of the females with TS and 16% of children considered ISS [Malaquias et al., 2013]. However, only Sitting height/Height ratio (SH/H) was investigated. In our study, it was not possible to accurately determine sitting height, neither manually, nor with the aid of photogrammetric anthropometry. Since children with KS often have difficulty with maintaining a certain pose for accurate manual measurement, sitting height was proven to be inaccurate. In a previous study we investigated if sitting height could be determined on a photograph, however this lead to imperfect results [Penders et al., 2015]. However, with the aid of photogrammetric anthropometry, we were able to examine other anthropometric ratios, that gave us an elaborate overview of the body proportions of these children.

It is known that in many skeletal dysplasias, growth of the legs, and arms is often more negatively affected than growth of the trunk [Hagenäs and Hertel, 2003]. Interestingly, we found that in children with KS arm length was proportionately longer compared to trunk length. No significant difference were found between groups for tibia length proportional to trunk length.

When SHOX gene defects are present, shortening of the extremities is a main cause of short stature. In these children, the arm span and leg length is significantly reduced in comparison to the height [Ross et al., 2001; Binder et al., 2003]. In children with KS we found no significant differences in arm length proportional to height compared to normally proportioned children, although tibia length was significantly shorter proportional to their height.

Body proportions in TS have been described in untreated girls with between 2–11 years of age. Since height is more affected in these children than other parts of the body, these girls have, on average, a relatively large trunk, large hands and feet, and relatively large biacromial width and biiliacum width proportional to their height [Sas et al., 1999]. In the children with KS we found that they had, on average, a relatively small trunk compared to normally proportioned controls. Also, we found no significant differences in biacromial width and biiliacum width proportional to height between the children with KS and the reference group.

Apart from SH/H ratio, body proportions have not been elaborately described in children with idiopathic short stature. Therefore comparison of body proportions to the children with KS in this study is not yet possible.

In future studies we will compare body proportions in KS with other conditions in which short stature and skeletal anomalies are

present. It will be interesting to determine if the proportional ratios presented in this study can also be used to differentiate various skeletal anomalies in children from each other.

CONCLUSION

To our best knowledge, this is the first report on body proportions in Kabuki syndrome. It is shown here that various body ratios in KS clearly deviate from normally proportioned children. The key differences in body proportions in KS are that these children have larger heads and longer arms proportional to their trunks and longer upper arms proportional to their tibia length and feet. Knowledge of these body proportions in KS is valuable, since it can strengthen the clinical diagnosis and provide the means to follow up on the body proportions during growth and development.

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