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Exploring the cognitive phenotype of Kabuki (Niikawa–Kuroki) syndrome

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Abstract

Background Kabuki syndrome (KS) is a Mendelian disorder, characterised by short stature, facial dysmorphisms and developmental delay and/or intellectual disability. Clarification of the neurocognitive profile in KS may provide directions for education and treatment interventions for KS. Previous studies on cognitive functioning in KS are scarce and have mainly focused on the general level of intelligence. The few more extensive studies suggested weaknesses in language skills, visuoconstruction, perceptual reasoning and speed of information processing. Other relevant domains such as memory, executive functioning and social cognition have not been studied yet.
Method This is the first study in which cognitive functioning within multiple domains is systematically explored in 29 participants with KS (age range: 5–48 years) and compared to both norm groups (healthy population) and an appropriate control group of 15 individuals with other genetic syndromes (age range: 6–28 years).
Results Compared to the norm groups of the cognitive test manuals, as expected, participants with KS show a weaker performance on all cognitive tests. Comparison with the more appropriate genetic control group indicates weaknesses in visuoconstruction and visual memory and no weaknesses in planning, cognitive flexibility or social cognition. Verbal memory seems to be a relative strength.
Conclusions Individuals with KS suffer from specific weaknesses in visuoconstruction, in addition to their intellectual disability/developmental delay. These impairments in visuoconstruction plausibly result from problems in visual perceptual processing, which highlight the importance of the use of auditory cues instead of visual cues in targeted educational support and psychosocial interventions.

Keywords case–control study, cognition, contextual neuropsychology, Kabuki syndrome, KMT2D, neurodevelopmental disorder

Introduction

The neurodevelopmental Mendelian disorder Kabuki syndrome (KS; OMIM #147920) was first described in 1981 by two independent research

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groups (Kuroki *et al*. 1981; Niikawa *et al*. 1981). It is caused by heterozygous mutations in the *lysine-specific methyltransferase 2D* (*KMT2D*) gene (OMIM #602113) (Ng *et al*. 2010) or the *lysine-specific demethylase 6A* (*KDM6A*) gene (OMIM #300867) (Lederer *et al*. 2012; Miyake *et al*. 2013). Although the current prevalence is unknown, an earlier study indicated a prevalence of 1 in 32 000 new-born infants in Japan (Niikawa *et al*. 1988). KS is characterised by developmental delay and/or intellectual disability (ID), short stature and typical craniofacial features such as long palpebral fissures with an eversion of the lower eyelid, long dense eyelashes and arched eyebrows. People with KS frequently have microcephaly, congenital heart defects, urinary tract anomalies, skeletal abnormality, recurrent upper airway infections, fetal finger pads and abnormality in the dermatoglyphic pattern (Philip *et al*. 1992; Schrander-Stumpel *et al*. 1994; Adam and Hudgins 2005; Bögershausen & Wollnik 2013). Furthermore, the syndrome is associated with hearing and vision impairments. Hearing difficulties are probably a result of the frequently occurring middle ear infections in KS. Although severe visual impairments are rare, 38–61% of the individuals with KS display ocular abnormalities such as strabismus, blue sclera, ptosis, coloboma of the iris and retina and refractive anomalies (Bögershausen & Wollnik 2013).

Multiple studies describe both structural and functional anomalies of the brain in KS. Brain aberrations are generally non-specific and are reported in approximately 40% of the individuals. These comprise mostly agenesis/hypoplasia of the corpus callosum, but hydrocephalus, cerebellar anomalies, cortical and central hypoplasia, ventricular dilatation, generalised brain atrophy, and white matter abnormalities have been reported as well (Ben-Omran & Teebi 2005; Li *et al*. 2011). As for impairments in brain functioning, epileptic seizures have been described in 5–36% of the individuals, mostly characterised as focal, but bilateral convulsive and myoclonic seizures have also been reported (Li *et al*. 2011; Kurahashi *et al*. 2017; Lehman *et al*. 2017). Interictal electroencephalography has most frequently revealed focal paroxysmal epileptiform discharges in regions including fronto-central, parietal, fronto-temporal and temporo-occipital areas. Mixed results were found for the effects of treatment with antiepileptic drugs: the majority of people were not immediately responsive to medication in one study, whereas one other study reported efficient pharmacotherapy in 80% of the individuals (Oksanen *et al*. 2004; Lodi *et al*. 2010; Verrotti *et al*. 2011; Kurahashi *et al*. 2017).

The level of intellectual functioning in KS ranges from severe ID to normal levels of intelligence, with the majority of the reported individuals displaying a mild to moderate ID (TIQ range: 35–69; Bögershausen & Wollnik 2013, Lehman *et al*. 2017). Knowledge of the specific strengths and weaknesses in cognitive functioning in individuals with KS, additional to the level of intelligence, is important for the development of interventions in KS. Targeted educational support for instance, may be helpful for people with KS. Understanding the cognitive profile in KS is essential in order to implement this type of support in daily practice. Although most studies of KS include descriptions of developmental delay or ID, there is a lack of studies that focus on cognitive functioning in more detail. The few studies that did include measurements of cognitive functioning only focused on language abilities (Morgan *et al*. 2015) and visuoconstruction (Caciolo *et al*. 2018), indeed displaying specific weaknesses in these domains, or included a global cognitive screening based on a battery of standardised intelligence tasks (Mervis *et al*. 2005; Lehman *et al*. 2017). Index scores for verbal comprehension and working memory were found to be higher in children with KS in the cognitive screening study than those for perceptual reasoning and processing speed (Lehman *et al*. 2017). Although this study provides hypotheses regarding weaknesses in perceptual processing, they should first be validated with traditional measures of the domains of cognitive functioning.

None of the aforementioned cited studies included a suitable control group to establish possible strengths and weaknesses in individuals with KS. In these studies, performances of individuals with KS were either compared to performances of other people with KS (e.g. the comparison of a group of individuals with a genetically confirmed diagnosis to a group with a clinical suspicion of KS but without the molecular confirmation) or compared to a norm group of individuals with average levels of intelligence (the majority of individuals in norm groups representing 'the healthy population'). However, a comparison of

individuals with KS using controls with a similar level of intelligence is essential for adequate interpretation of neuropsychological data, as individuals with ID will likely deviate on all domains of cognitive functioning compared to controls with average intelligence levels (e.g. Lezak *et al*. 2012; Fletcher *et al*. 2017). Specific cognitive weaknesses or potential strengths related to KS will otherwise remain unnoticed.

Thus, previous studies regarding cognitive functioning in KS did not include an appropriate control group nor included important domains of neurocognitive functioning such as memory and executive functioning. Therefore, the present study examines multiple cognitive domains in a substantial group of participants with KS (n = 28) in order to clarify the neurocognitive profile of KS. Performances on measures of intelligence, adaptive functioning, memory, executive functioning, social cognition and visuoconstruction in participants with KS will be compared to both the norm group represented in the manuals of the cognitive tests and to the performance of an appropriate control group. The latter consists of a mixed group of individuals with other genetic syndromes that are accompanied by ID/developmental delay.

Method

Participants

This study included 28 participants with KS (KS group; 15 male participants; age range: 5–48 years) and 15 control participants with another genetic disorder (GC group; seven male participants; age range 6–28 years). Participants with KS were recruited for the study by clinical geneticists at the Dutch expertise centre for KS (Maastricht University Medical Centre, The Netherlands) and with help from the Kabuki caretakers network group in the Netherlands. Table 1 presents the medical characteristics (ocular problems, hearing problems as well as brain functioning and psychopharmacotherapy) of the

Table 1 Medical characteristics of participants with Kabuki syndrome

Domain	*n*	Specification
Ocular problems	17	Minor problems successfully compensated by glasses or disturbed stereoscopic vision/strabism
	4	Severe problems: total loss of sight in one eye for all four participants and for three of them additionally a loss of 50% in the other eye[1], loss of 85% and tube vision in the other eye[1], and nystagmus[2]
Hearing problems	3	Single sided deafness
	7	Minor hearing problems were present without a need for hearing aids
	9	Hearing problems that were successfully compensated by hearing aids
	7	Hearing problems that were not sufficiently compensated by hearing aids. Hearing was however still sufficient for cognitive assessment
Brain imaging reports	-	Reports present for three participants; these did not show any structural anomalies, besides microcephaly in one participant
Possible neural damage as a result of brain trauma	3	Oxygen shortage during birth [1], cerebrovascular accident [2], oxygen shortage as a result of low blood sugar [2]
Brain functioning	1	History of epileptic seizures, currently in remission with the use of Depakine
Psychopharmacotherapy	3	Antipsychotics (aripiprazol, risperidon and Dipiperon)
Sleep medication	5	Melatonin
Hormone treatment	9	-

[1]Participant of the KS-B group.
[2]Participant of the KS-A group.

KS group. Individual demographical variables and genetic aberrations are displayed in Table S1. Not all participants with KS were able to execute the entire cognitive assessment. These participants are referred to as the 'KS-A' group (n = 10). The other participants with KS completed at least the intelligence battery plus one test of each specific cognitive domain, and they will be referred to as the 'KS-B' group (n = 18). The GC group included a convenience sample of individuals with other genetic disorders who visited the expertise centre for rare genetic neurodevelopmental disorders (Radboud University Medical Centre, The Netherlands). The study was conducted according to the Declaration of Helsinki and approved by the Central Committee on Research Involving Human Subjects region Arnhem-Nijmegen (NL43187.091.13) with written informed consent obtained from all participants, or their legal representatives.

Materials and procedure

To facilitate participation, individuals were visited at their homes for the assessment. Testing was performed by a trained and experienced (>4 years) psychologist and took place in two visits of approximately 4 h, in which breaks were provided based on the individual needs of each participant. To measure adaptive functioning, primary caregivers of the participants were interviewed, using the Vineland-Z (Dutch version of the Vineland Adaptive Behavior Scales Survey Form; Sparrow *et al.* 1984). Adaptive functioning refers to the conceptual, social and practical skills that have been learned by people in order to function in everyday life (American Association on Intellectual and Developmental Disabilities 2018). The Vineland-Z total level of adaptive functioning is expressed in a developmental age. Secondly, a measure of visual and motor abilities as well as visuoconstruction was included (Beery–Buktenica Developmental Test of Visual-Motor Integration; Beery VMI; Beery & Beery 2004). Intelligence was measured with the Wechsler Adult Intelligence Scale-IV-NL (WAIS-IV-NL, Dutch version of the WAIS-IV; Wechsler 2008; Wechsler 2012) for adults, or the WISC-III-NL (Dutch version of the WISC-III; Wechsler 1991; Wechsler 2005) for children. Cognitive flexibility and planning were assessed by the Intra/Extradimensional shifting task (Cambridge Neuropsychological Test Automated Battery, CANTAB®) [Cognitive assessment software] 2018), Key search task and Zoo map task (both part of the Behavioural Assessment of the Dysexecutive Syndrome battery; Wilson *et al.* 1996; Emslie *et al.* 2003). Furthermore, memory functioning was measured by the Rey Auditory Verbal Learning Test (RAVLT; Schmand *et al.* 2012, Osterrieth 1944), Paired Associates Learning test (PAL, CANTAB®) and Pattern Recognition Memory test (PRM, CANTAB®). As for social cognition, performance was assessed by the Dutch Theory of Mind test-Revised (Steerneman 2009). All tests are commonly used in a variety of international neuropsychological studies. For a more extensive description of the tests, see Table S2.

Statistical analysis

SPSS version 22 for Windows was used for all statistical analyses. First, mean developmental age scores were calculated based on the norm group in the manual of the VABS, to describe adaptive functioning in the total KS sample as well as for both KS groups (A and B) separately. Secondly, in order to explore the more extended cognitive profile, performances of the KS-B group on the Wechsler scales, intra/extradimensional shifting test, Key search task, Zoo map task, RAVLT, PAL, PRM, Theory of Mind test-Revised, emotion recognition and Beery were compared to the results of norm groups described in the test manuals (via transformation of raw scores into standardised scores). Finally, cognitive test performances of the KS-B group were compared to those of the GC group. Although a general linear model repeated measures would have been the preferred choice for this design, this was not feasible due to a lack of power as a result of the relatively small sample size compared to the large number of dependent variables. The use of this statistical test would therefore not be informative in this sample. Instead, Cohen's d was calculated for all differences in cognitive test performances between both groups (Cohen 1992; Lee 2016).

Results

Table 2 displays the means and standard deviations for adaptive functioning in the total KS group and for

Table 2 Chronological age and developmental age for Kabuki syndrome groups

	KS total			KS-A			KS-B		
	28 (15)			10 (7)			18 (8)		
***N* (male participants)**	***M***	***SD***	**Range**	***M***	***SD***	**Range**	***M***	***SD***	**Range**
Chronological age [1]	206.4	133.4	63–577	145.9	159.5	63–577	240.1	*107.0*	72–461
Developmental age [2]	61.9	38.7	13–145	29.6	13.5	13–49	79.78	*36.5*	25–145

[1]Age in months.

[2]Based on normative means of the Vineland Z, in months.

the KS-A and KS-B groups separately. A large difference between chronological and developmental age was present in all three groups. Furthermore, the mean developmental age is substantially higher in the KS-B group compared to the KS-A group, in accordance with the fact that the KS-B group was able to complete more (complex) cognitive tasks. Individual intelligence scores and levels of adaptive functioning of participants with KS are displayed in Table S1.

For the comparison of the KS-B group with healthy individuals, Table 3 presents the mean differences (IQ and T-scores) between participants with KS and the available norm groups for all cognitive tests. As expected, the KS-B group showed a weaker performance on all of these tests. The mean performance on the cognitive domains ranged between 1.2 and 2.9 standard deviations below the healthy population. Weakest performances were present in the domains of intelligence and visuoconstruction.

Table 4 displays the mean raw scores and effect sizes for the comparison of the results of the KS-B and GC group. The general level of intelligence for the GC group (M = 66.6, SD = 13.7) was higher than for the KS-B group (M = 55.6, SD = 10.1; Cohen's d = −.92). Furthermore, visuoconstruction was weaker in the KS-B group (Beery VMI: M = 13.7, SD = 3.6; Beery Visual: M = 17.2, SD = 4.1; Beery Motor: M = 14.9, SD = 6.3) compared to the GC group (Beery VMI: M = 19.1, SD = 4.9; Cohen's d = −1.29; Beery Visual: M = 21.6, SD = 4.5; Cohen's d = −1.05; Beery Motor: M = 21.1, SD = 5.3; Cohen's d = −1.10). As for memory

Table 3 Cognitive performances in KS-B group compared to the norm groups of the test manuals

		N	**Devination from the norm group (in *SD*)**	**Classification**
Intelligence	WAIS-IV/WISC-III [1]	18	−2.96	Low
Memory	RAVLT immediate recall [1,2]	18	−1.09	Low average
	RAVLT delayed recall [1,2]	17	−1.61	Below average
Executive functioning	Key search [1]	16	−1.2	Low average
	Zoo map 1 [1]	15	−1.36	Below average
	Zoo map 2 [1]	15	−1.56	Below average
Social cognition	ToM test-R [1,2]	16	−1.66	Below average
Visuoconstruction	Beery VMI [1]	18	−2.97	Low

[1]Normative means corrected for age.

[2]Maximum age of the normative means was 12 (RAVLT, ToM test-R) or 16 (Key search, Zoo map) years of age.

Key search, Zoo map 1 and Zoo map 2 are subtests of the Behavioural Assessment of the Dysexecutive Syndrome. Beery VMI, Beery–Buktenica Developmental Test of Visual-Motor Integration; ToM test-R, Theory of Mind test-Revised; RAVLT, Rey Auditory Verbal Learning Test; WAIS-IV, Wechsler Adult Intelligence Scale-Fourth Edition; WISC-III, Wechsler Intelligence Scale Children-Third Edition.

Table 4 Comparison KS-B and GC

		KS-B			GC				
		N	*M* [1]	*SD* [1]	*N*	*M* [1]	*SD* [1]	Mean difference	Effect size[2]
Intelligence	TIQ	18	55.6	10.1	22	66.6	*13.7*	−11.0	−.92
Executive functioning	IED	17	6.8	2.4	20	7.0	*2.4*	−.2	−.09
	Key search	17	4.9	4.5	20	3.8	*4.4*	1.1	.25
	Zoo map 1	16	−2.4	6.0	19	−1.3	*4.7*	−1.1	−.21
	Zoo map 2	16	2.8	6.1	19	3.2	*5.4*	−.4	−.07
Memory	RAVLT immediate recall	18	37.4	10.1	21	33.5	*11.0*	3.9	.38
	RAVLT delayed recall	17	6.5	3.4	20	6.2	*3.2*	.3	.09
	PRM	17	8.1	2.9	20	9.7	*1.9*	−1.6	−.68
	PAL	17	5.6	1.9	20	6.6	*1.6*	−1.0	−.59
Social cognition	ToM test-R	16	25.4	6.0	21	24.8	*5.6*	.6	.11
Visuoconstruction	Beery VMI	18	13.7	3.6	18	19.1	*4.9*	−5.4	−1.29
	Beery Visual	18	17.2	4.1	18	21.6	*4.5*	−4.4	−1.05
	Beery Motor	18	14.9	6.3	18	21.1	*5.3*	−6.2	−1.10

[1]Raw performance scores.

[2]Cohen's *d* effect sizes of .2, .5 and .8 represent, respectively, a small, medium and large effect.

Key search, Zoo map 1 and Zoo map 2 are subtests of the Behavioural Assessment of the Dysexecutive Syndrome; Beery VMI, Beery–Buktenica Developmental Test of Visual-Motor Integration; IED, intra/extradimensional shift test (CANTAB); PAL, Paired Associates Learning test (CANTAB); PRM, Pattern Recognition Memory test (CANTAB); RAVLT, Rey Auditory Verbal Learning Test; ToM test-R, Theory of Mind test-Revised; TIQ, total intelligence quotient.

functioning, mixed results were found. Weaknesses in performances were found on two tests of visual memory in the KS-B group (PRM: $M = 8.1$, SD = 2.9; PAL: $M = 5.6$, SD = 1.9) compared to the GC group (PRM: $M = 9.7$, SD = 1.9; Cohen's $d = -.68$; PAL: $M = 6.6$, SD = 1.6; Cohen's $d = -.59$). While a slightly higher performance was present in the KS-B group for a task that taps into verbal memory (RAVLT immediate recall: KS-B: $M = 37.4$, SD = 10.1; GC: $M = 33.5$, SD = 11.0; Cohen's $d = .38$). As for other domains of cognitive functioning, there were no relevant differences between the KS-B and GC group in planning, executive functioning or social cognition ($-.21 <$ Cohen's $d < .25$).

Discussion

This is the first case–control study to explore multiple domains of cognitive functioning in individuals with KS. Performances of intelligence, executive functioning, memory, social cognition and visuoconstruction in participants with KS (KS-B group) were first compared to the results of norm groups represented in the manuals of the different cognitive tests. As expected, performances of the KS-B group were lower than those of norm groups consisting of healthy people, for all cognitive tests. Participants within the KS-B group deviated most strongly on the domains of intelligence and visuoconstruction, in contrast to a relatively small deviation for the domains of executive functioning, memory and social cognition. These results could indicate that these last domains are relatively unaffected in participants with KS, in spite of their intellectual impairment. Performances of the KS-B group were then compared to those of a more appropriate control group, to further sustain these findings. The latter group consisted of participants with other genetic syndromes associated with ID/developmental delay.

A lower mean level of intelligence was present for the KS-B group compared to the GC group. Nonetheless, there were no substantial differences in performances between the KS-B group and PGC group on domains of executive functioning, verbal memory and social cognition. The latter result was also in accordance with the comparison between the KS-B and the norm group, which might indicate a

relative strength of these cognitive domains in individuals with KS. Furthermore, lower performances in the KS-B group compared to the GC group were present for the domains of visuoconstruction and visual memory. As verbal memory was relatively unaffected in the KS-B group, the visual memory problems may have been a result of weaknesses in visual processing interfering with imprinting, rather than a result of genuine memory problems.

Multiple factors could have contributed to the weaknesses found in visuoconstruction in the KS-B group. First of all, it may have been a result of ocular anomalies. As the majority of participants had only minor ocular problems, which probably did not interfere with cognitive test performances, group results may plausibly have been affected by only three of the participants (with more severe ocular problems). Their performances did not deviate substantially more from the group mean than the performances of other participants in the KS-B group, which suggests only a minor negative influence on the total group performances. Secondly, lower scores on tasks measuring visuoconstruction could have been the result of primary deficits in motor responses, for instance due to hypotonia or developmental delay of fine motor skills, which have often been reported in participants with KS (Bögershausen and Wollnik 2013). A weaker performance was indeed found on a task that taps explicitly into fine motor functioning (Beery Motor). However, these weaknesses did not entirely explain the differences in visuoconstruction between the KS-B and GC group, which argues for additional cognitive weaknesses. The visuoconstruction problems may have been a reflection of the initial differences in intellectual functioning between the KS-B and GC groups, although they seem to be too specific to be explained by the differences in intellectual functioning entirely. Thus, it is plausible that our results reflect specific weaknesses in primarily visual perceptive processing (and as a result also in visuoconstruction), which is in line with previous findings of weaker performances of participants with KS on tasks that tap into visual perceptive processing (Lehman *et al.* 2017; Caciolo *et al.* 2018). Future studies may focus on the development of specialised interventions for these visual processing problems in KS.

The strengths of the current study lie in the extensiveness of the cognitive assessment and the inclusion of a genetic control group, which enables the observation of specific strengths and weaknesses related to KS. Not all participants were able to execute the entire assessment, which resulted in an exclusion of these individuals for the analyses of cognitive performance. As expected, results on measures of adaptive functioning indicated that developmental age was higher in the KS-B group compared to the KS-A group. Because the results on cognitive tasks were solely based on performances of the KS-B group, findings may therefore reflect an overestimation of the capabilities of the total population of individuals with KS.

This study was executed parallel to another study on cognitive functioning in KS (Harris *et al.* 2019). Design, data collection and interpretation of the results of that study, however, were performed independently and none of the participants was included in both samples. Interestingly also in this complementary study, weaknesses in similar domains were notified, further emphasising our findings.

In conclusion, this study indicates that individuals with KS suffer from specific weaknesses in visuoconstruction and visual memory, additional to general ID. The visuoconstruction problems that were demonstrated may well reflect a primary problem in visual perceptual processing, which may also be the underlying cause of the observed weaknesses in visual memory. Contrary to the use of visual symbols, often applied in the daily practice of patient care for individuals with ID, the results presented here highlight the importance of the use of auditory cues instead of or additional to visual cues, in targeted educational support and psychosocial interventions for individuals with KS.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1: Characteristics of participants with KS

Table S2: Details and references of cognitive measures