Case Report

Cytogenetic and Genome Research

Cytogenet Genome Res 2016;150:40–45
DOI: 10.1159/000452724

Accepted: July 25, 2016
by M. Schmid
Published online: November 17, 2016

Koolen-de Vries Syndrome: Clinical Report of an Adult and Literature Review

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Key Words
17q21.31 · Deletion · Joint hypermobility · *KANSL1*

Abstract
Koolen-de Vries syndrome (KdS) is a rare genetic condition characterized by typical facial dysmorphisms, cardiac and renal defects, skeletal anomalies, developmental delay, and intellectual disability of variable level. It is caused by a 440–680-kb deletion in the 17q21.31 region, encompassing *CRHR1*, *MAPT*, *IMP5*, *STH*, and *KANSL1*, or by an intragenic *KANSL1* mutation. The majority of the patients reported are pediatric or young adults, and long-term studies able to define the prognosis of the disease are lacking. Here, we report a patient in the fourth decade misdiagnosed in the past as classical Ehlers-Danlos syndrome for the presence of generalized joint hypermobility, who carried a 546-kb deletion in 17q21.31, and compare his phenotype with those of the few KdS adults (aged >18 years) described so far. We observed a favorable prognosis of epilepsy and cardiovascular signs and reduction of joint hypermobility with age, thus providing insight into the natural history of the disorder.

Koolen-de Vries syndrome (KdS, also known as 17q21.31 microdeletion syndrome, OMIM #610443) is a rare genetic disorder (prevalence 1/16,000) characterized by typical facial dysmorphisms, cardiac and renal defects, developmental delay, and intellectual disability of variable level [Tan et al., 2009]. The disorder was initially described as a form of mental retardation caused by a 440–680-kb deletion in the 17q21.31 region, typically encompassing 5 genes: *CRHR1* (OMIM *122561), *MAPT* (OMIM *157140), *IMP5* (OMIM *608284), *STH* (OMIM *607067), and *KANSL1* (OMIM *612452) [Koolen et al., 2006]. Recently, it has been shown that haploinsufficiency of *KANSL1* by itself, due to single nucleotide variants or gene deletion, is sufficient to cause the full-blown phenotype of the disorder [Zollino et al., 2012, Koolen et al., 2016]. All the subjects show global developmental delay; most of them are not able to walk independently before the age of 36 months, and good language skills are generally reached around the 4th year of life. Cognitive impairment is always present and can vary from mild to severe [Zollino et al., 2015]. Epilepsy or seizures are observed in about 50% of the patients, and they are variously associated with abnormal brain MRI findings (periventricular and perivascular matter enlargement, corpus callosum or hippocampal dysplasia, thin pituary stalk) or with elec-

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troencephalography anomalies [Terrone et al., 2012, Koolen et al., 2016]. Congenital cardiac defects (pulmonary stenosis 27%, septal defects 18%, bicuspid aortic valve 18%, patent ductus arteriosus or foramen ovale), acquired aortic dilatation, and urologic anomalies (82%, including cryptorchidism, hypospadias, vesicoureteral reflux) are commonly found. Most of the patients (58–73%) show joint hypermobility (JHM) during childhood, sometimes leading to hip dislocations (congenital or acquired) or positional deformities of the feet [Tan et al., 2009, Koolen et al., 2016]. Additional features may include short stature according to genetic target, hearing loss (conductive, sensorineural or mixed, 26%), ectodermal abnormalities, hypermetropia, and other ocular defects [Zollino et al., 2015, Koolen et al., 2016].

The majority of described patients are in infants or adolescents, and currently only 9 patients aged >18 years are reported in large-cohort studies. Here, we report an additional adult patient and provide a review of the adult phenotype of KdS.

Case Report and Methods

The patient, a 40-year-old man, came to our attention with a clinical diagnosis of classical Ehlers-Danlos Syndrome (cEDS), given in 1992 at the age of 17 and never been refuted. He was born at 44 weeks of gestation, perinatal distress was not referred, and psychomotor development was delayed. At 6 years of age, he developed idiopathic generalized epilepsy well-controlled by antiepileptic drugs; brain abnormalities were not recognized at MRI. Seizures gradually decreased in severity, and therapy had been definitively discontinued at the age of 13. Generalized JHM was referred to be present during childhood and complicated by 2 episodes of joint dislocation. Heart ultrasound, performed at the age of 40 years, revealed mitral valve prolapse without valve insufficiency and mild aortic bulb dilatation (4.34 cm, z-score 3.93); previous cardiac evaluations were not available. Consistently with the typical KdS phenotype, clinical assessment at 40 years of age showed a moderate cognitive impairment with a global IQ of 48 (evaluated with WAIS-R) [Wechsler, 1997]. Anxiety, poor eye contact, and difficulty to perform activity of daily living (ADL) were also observed. At physical examination facial dysmorphisms (fig. 1a, b), xerosis on the lower limbs, absence of JHM according to Beighton score, and several skeletal alterations, i.e., scoliosis, cubitus valgus, andarachno-clinodactyly, minor asymmetry at lower limbs, pes planus, and hallux valgus (fig. 1c–e) were recognized. His height was slightly under the genetic target (163 cm, genetic target based on parents' height of 171 cm), and the BMI was within the normal range (22).

Notably, cutaneous signs typical of cEDS (skin hyperextensibility, atrophic scars) [Ritelli et al., 2013] were absent and the patient did not fulfill the criteria to pose a clinical diagnosis of the disorder [Beighton et al., 1998]. Thus, we excluded the diagnosis of cEDS. Microarray-based comparative genomic hybridization (aCGH) was performed in an external laboratory using an oligonucleotide array with an average spacing of 13 kb (180 k; Human Genome Building 37, Hg19, Assembly February 2009, Agilent Technologies). Microarray data were analyzed with the Cytogenomics software (v2.7; Agilent Technologies) using the ADM-2 algorithm that showed a 546-kb deletion in 17q21.31, encompassing the 5 genes involved in 17q21.31 microdeletion syndrome, i.e., *CRHR1*, *MAPT*, *IMP5*, *STH*, and *KANSL1* (not shown). Parental array analysis showed normal results, confirming that the deletion occurred de novo.

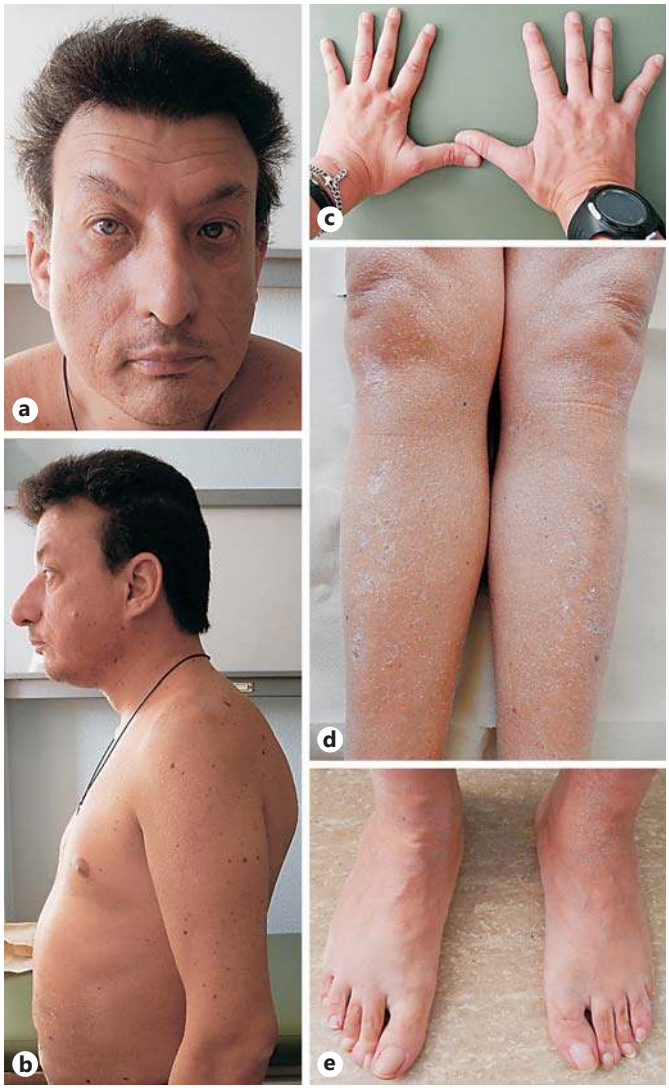

Fig. 1. Clinical features of the 17q21.31 microdeletion syndrome patient. **a**, **b** Typical facial appearance with long face, inverse epicanthal folds, low-set ears with hypoplastic auricular lobe, tubular nose, and microretrognathia. **b** Skeletal anomalies like scoliosis with gibbus deformity, cubitus valgus. **c** Pachydermodactyly. **d** Cutaneous xerosis of pretibial region and atrophic scars. **e** Pes planus, bilateral arachno-clinodactyly of the toes, and hallux valgus.

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Table 1. Clinical and molecular findings of adult patients affected by Koolen-de Vries syndrome reported so far

	P1, present case	P2	P3	P4	P5	P6	P7	P8	P9	P10
Gender	male	male	female	female	male	female	male	male	male	female
Age, years	40	20	27	32	43	50	23	31	20	46
Genetics	17q21.31 microdeletion	17q21.31 microdeletion	17q21.31 microdeletion	17q21.31 microdeletion	17q21.31 microdeletion	17q21.31 microdeletion	17q21.31 microdeletion	17q21.31 microdeletion	c.3125del in *KANSL1*	c.908_909del in *KANSL1*
Gestational age, weeks	44	40	42	41	40	46	n.a.	n.a.	40	40
Birth weight, g	2,700 (–2 SD)	2,700 (–2 SD)	3,950 (+0.5 SD)	2,200 (–2.5 SD)	growth delay	3,100 (–1.3 SD)	3,800	4,500	3,180 (–0.3 SD)	3,750 (+0.5 SD)
Height, cm	163 (–2.50 SD)	167 (–2.37 SD)	165 (–0.92 SD)	160 (–1.72 SD)	166.4 (–2.43 SD)	155 (–2.51 SD)	156 (–3.5 SD)	n.a.	170.4 (–0.88 SD)	168 (–0.44 SD)
Postnatal short stature	+	+	–	–	+	+	+	n.a.	–	–
Weight, kg	68	n.a.	66	73	n.a.	52	39	n.a.	n.a.	n.a.
BMI	22	n.a.	24.2	28.5	n.a.	21.6	16.2	n.a.	n.a.	n.a.
Neurological/neuropsychological features										
Hypotonia	–	+	+	+	–	+	+	+	–	+
Feeding problems	–	+	+	+	–	+ in infancy	–	–	–	+
Intellectual disability	moderate	severe	severe	moderate	moderate	n.a.	moderate	moderate	mild	moderate
Intelligence quotient (IQ)	48	n.a.	55	46	35	n.a.	n.a.	n.a.	61	n.a.
Seizures/EEG anomalies	+ in infancy	+ Lennox Gastaut	+	+	–	–	+	–	+	–
Enlarged ventricles and hydrocephalus	–	+	+	n.a.	–	–	–	–	–	–
Other structural CNS anomalies	–	+[a]	+[b]	–	+[c]	–	–	–	–	+[d]
Friendly/amiable affect	–	+	+	+	–	+	+	+	+	+
Stereotypic behavior	–	+	+	–	–	+	+	–	+	–
Anxiety	+	–	+	–	+	+	–	–	+	–
Difficulty to perform ADL	+	+	–	–	–	–	–	–	+ severe	–
Other	poor eye contact	poor eye contact	autism-like symptoms	psychosis		depression episodes		absent speech, high pain threshold	hypomimia	high pain threshold
Dysmorphic features										
Long face	+	+	+	+	+	+	+	+	+	+
Upslanting palpebral fissures	–	+	+	+	–	–	+	–	–	–
Ptosis	–	–	–	+	+	–	n.a.	–	–	+
Epicanthal folds	+	+	+	–	+	–	n.a.	–	–	–
Tubular or pear-shaped nose	+	+	+	+	+	+	+	+	–	+
Everted lower lip	–	+	+	–	+	+	+	+	+	–
Large/prominent ears	–	+	–	–	+	–	–	–	–	–
Other		brachycephaly			turricephaly		sparse eyebrow	sparse eyebrow		blepharo-phimosis

Table 1 (continued)

	P1, present case	P2	P3	P4	P5	P6	P7	P8	P9	P10
Hearing and visual impairments										
Hypermetropia	–	–	+	n.a.	+	–	n.a.	–	–	+
Strabismus	–	+	+	+	+	–	n.a.	–	–	+
Retinal impairment	+	–	+ left foveal scarring	–	–	–	–	–	–	–
Hearing impairment	+	+	+	+	–	+	–	–	–	–
Other		cerebral blindness			optic nerve subatrophy					
Musculoskeletal anomalies										
Tracheo/larynchomalacia	–	–	+	–	–	–	–	+	–	–
Pectus deformities	+ in infancy	+	–	–	–	–	+	–	–	–
Scoliosis/kyphosis	+	+	+	+	+	+	+		–	+
JHM at evaluation	–	–	+	+	–	+	+	+	–	+
Arachnodactyly/slender fingers	+	+	–	–	–	–	–	–	–	–
Positional deformity feet	+	+	+	+	–	–	–	+	–	+
Cubita/halluces/ genua valga	+	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	–	n.a.	n.a.
Minor body asymmetry	+	–	+	+	–	+	n.a.	–	–	–
Other	L5-S1 spondylo-listhesis	contractures, small hands		hernia, nuclei pulposi	large hallux	spina bifida L2				
Cardiovascular defects										
Atrial/ventricular septal defects	–	–	–	–	–	–	n.a.	–	–	+
Valvular defects	MVP	–	–	–	–	–	n.a.	–	–	+
Arterial ectasia/dilatation	+ (aortic bulb)	–	–	–	–	–	n.a.	–	–	–
Renal/urogenital anomalies										
Vesicoureteral reflux	–	+	–	–	+	–	–	–	–	+
Hydronephrosis	–	–	–	–	–	–	+	–	–	–
Cryptorchidism/ macrorchidism	–	+	–	–	+	–	–	–	–	–
Ectodermal abnormalities										
Multiple moles	–	–	–	+	–	+	–	–	–	+
Hyper/hypopigmentation	–	–	–	–	+	+	+	–	–	–
Dry skin/eczema	+	–	+	–	+	+	–	–	–	–
Other ectodermal abnormalities			hypohidrosis	small teeth	vitiligo					oligodontia

P7 and P8 are from Zollino et al. [2015], all other patients (P2–P6, P9, P10) are from Koolen et al. [2016].

ADL = Activity of daily living; JHM = joint hypermobility; MVP = mitral valve prolapse; n.a. = not available; SD = standard deviation. [a] Tetraplegia, atrofia cerebri, delayed myelinization. [b] Wide basal cisterna and cisterna magna, mild central and cortical atrophia. [c] Rear developmental delay on the corpus callosum. [d] Dural ectasia and cysts.

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Discussion

The present case is one of the few adults with KdS described so far. In particular, 7 adult patients (aged >18 years, range 20–50 years) are included in the series reported by Koolen et al. [2016] and 2 young adults (23- and 31-years-old) are described in the cohort reported by Zollino et al. [2015]. Clinical and molecular data of these patients are summarized in table 1.

Although some children affected by this condition experienced low weight gain in infancy, 4 patients, including ours, had a normal or slightly increased body mass index (BMI) at adult age, suggesting that the patients generally reach a normal weight in adulthood (table 1, BMI of 5 patients is unavailable). The height had a mean value of 163 cm (range 155–166.4) in the males and of 163.8 cm (range 155–170 cm) in the females; short stature (<2SD) was present in 5 patients (table 1). Regarding cardiovascular involvement, in our patient the mitral valve prolapse and the aortic bulb dilatation did not lead to hemodynamically significant valve insufficiency or cardiovascular events, supporting the idea that cardiovascular defects linked to this syndrome may have a slow progression. The other adult patients, except for P10, did not show any cardiovascular involvement (table 1). JHM at time of assessment was present in 2 out of 4 patients aged ≥40 years, among the patients aged ≤40 years JHM was observed in 4 out 6 patients (table 1). These findings fit with the regression trend of this sign in adult age observed in other syndromes with JHM [Jones et al., 2013; Colombi et al., 2015]. Therefore, JHM is not a diagnostic handle for KdS, considering that it may be potentially present in a large subset of genetic diseases. Thus, patients with JHM should be carefully investigated searching for more specific signs, i.e., connective tissue or cognitive impairment. In heritable connective tissue disorders usually a normal IQ is observed [Jones et al., 2013; Colombi et al., 2015]. Apart from intellectual disability, neurological involvement in KdS may include seizures. Our patient, diagnosed with idiopathic generalized epilepsy during childhood, achieved a seizure-free status since early adolescence. Seizures, generally well controlled with antiepileptic drugs, were described in other 5 adult patients, but no data about progression are available (table 1). In 3 adult patients, including ours, difficulties to perform ADL are reported, suggesting that, at least a part of the affected individuals, will probably require life-long support from caregivers. Neuropsychological disorders were frequently observed in adulthood ranging from anxiety (5/10), stereotypic/behavioral problems (5/10), to poor eye contact (2/10); psychosis was recognized in 1 patient (table 1). Among patients aged ≤18 years, attention deficit/hyperactivity disorder (ADHD or autistic trait) are reported [Koolen et al., 2016]. A friendly/amiable attitude was described in the majority of adult (8/10) and pediatric patients [Koolen et al., 2016]. Regarding dysmorphic features, all adult patients with KdS showed a long face. Among the patients aged ≤18 years the incidence of this signs is about 68–76% (23/30 in Zollino et al. [2012]; 26/38 in Koolen et al. [2016]), and it seems, as suggested by Koolen et al. [2016], that there is an elongation and coarsening of the face with age. Finally, the phenotype of the 8 adult patients with the 17q21.31 deletion appears indistinguishable from those observed in the 2 adults with pathogenic variants in *KANSL1*, suggesting a similar prognosis for both group of patients (table 1). The most disabling symptoms of KdS in adulthood appear to be related to the neuropsychological involvement mostly with anxiety, behavioral problems, cognitive impairment, and problems to perform ADL; epilepsy is generally absent or well-controlled, cardiovascular events and late onset diseases have not been reported so far.

Further reports from long-term studies are required to delineate the progression of KdS confirming the absence of late-onset diseases.

Acknowledgments

The authors thank the patient and his parents for the cooperation during the diagnostic process.

Statement of Ethics

Written informed consent was obtained from the patient. This report is based on data obtained through routine clinical care and is not considered research at our institution; research ethics was therefore not obtained.

Disclosure Statement

The authors have no conflicts of interest to declare.

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