Koolen de Vries syndrome: A challenge in clinical practice☆

Síndrome Koolen de Vries: un reto en la práctica clínica

Dear Editor:

Koolen-de Vries syndrome (KDVS, OMIM 610443) is a rare genetic disorder with an approximate prevalence of 1 per 16,000 live births, with no predominance of either sex. It is characterised by neonatal hypotonia, intellectual disability, dysmorphic features (high and broad forehead, long face, palpebral fissures with epicanthic folds, pear-shaped nose) that become attenuated over the years, and friendly behaviour. Central nervous system abnormalities are also found in 80% of cases, such as epilepsy (50%) and brain malformations (hydrocephalus and agenesis or dysgenesis of the corpus callosum), congenital heart defects (valvulopathies and septal defects) in 40–63% depending on the series, and urogenital anomalies (cryptorchidism, hypospadias, vesicoureteral reflux, hydronephrosis, etc.) in up to 70%.[1]

It was first described in 2006 as a recurrent microdeletion localised in chromosome 17q21.31, between 500 and 650 kb in length, that comprises up to five genes: *CRHR1, SPPL2C, MAPT, STH* and *KANSL1* (or *KIAA1267)*, in addition to two putative genes, MGC57346 and C17orf69. In most cases, these are de novo mutations. Although the role of these genes in the pathogenesis of this disease remains unclear, recent studies have demonstrated that both *KANSL1* haploinsufficiency or point mutations are sufficient to produce the disease.[2–4] The most recently published case series (with 45 patients) described that while the phenotype is not significantly different based on whether there is a 17q21.31 microdeletion or a nonsense mutation of the *KANSL1* gene, there is wide phenotypic variability between individuals.[4]

Table 1 Case characteristics.

	Case 1	Case 2	Case 3	Case 4
Presenting complaint	Language delay	Psychomotor delay	Epilepsy	Delayed postural control
Phenotype	Dolichocephaly, long face, low-set prominent ears and bulbous nose	Hypertelorism, broad nasal root, long philtrum, low-set anteverted ears, broadly spaced nipples and mild pectus excavatum	Skull disproportionate to face, broad forehead and low-set ears	Long face, hypertelorism, epicanthic folds and low-set ears
Language	Monosyllabic	Absent No verbal language	Language delay	Poor, with difficulty in verbal expression
Intellectual disability	Yes	Yes	Yes	Yes
Behaviour	Friendly, but with difficulty in communicating with peers	Sociable	Friendly Hyperactivity	Affable Attention deficit
Epilepsy	No	Yes	Yes	No
Brain MRI	Hypogenesis of corpus callosum	Hypoplasia of posterior corpus callosum	Ventriculomegaly in the absence of hydrocephalus. Cortical and subcortical atrophy	Very mild cortical and subcortical atrophy
Karyotype	Normal	Normal	Normal	Normal
Fragile X	Normal	Normal	Normal	Normal
Array CGH	1600 kb microdeletion in the 17q21.31 band affecting up to 13 genes, including *MAPT* and *KANSL1*	Deletion of chromosome 17q21.31 (tested in a different facility)	621 kb microdeletion in 17q21.31 affecting the *CRHR1, IMPS, MAPT, STH* and *KANSL1* genes	695 kb microdeletion in 17q21.31 affecting the *C17of69, IMP5, MAPT, STH* and *KANSL1* genes
Echocardiogram	Normal	Bicuspid aortic valve	Normal	Normal
Renal ultrasound	Normal	Normal	Normal	Normal
Other		Short statute		Father with inversion polymorphism

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Table 2 Comparison of the most relevant characteristics found in the most recently published series and in our patients.

	Koolen, 2008 (%) *N* = 22	Zollino, 2015 (%) *N* = 32	Koolen, 2016 (%) *N* = 45	Our series (%) *N* = 4
Dysmorphic features				
Long face	74	75	75	50
Bulbous nose	82	93.7	88.3	50
Prominent ears	59	–	32.6	75
Everted lower lip	–	93.7	71.4	0
Epicanthic fold	68	–	52.3	50
Macrocephaly	–	40	14.3	25
Neurologic features				
Hypotonia	96	100	86.4	50
Intellectual disability	–	90	100	100
Motor delay	100	–	97.3	75
Language delay		87	100	100
Epilepsy	50	50	48.9	50
CNS structural malformations	–	50	52.9	75
Friendly/amiable behaviour	89	95	88.7	100
Musculoskeletal anomalies	25	40	76.7	25
Heart defects	27	35	38.6	25
Renal/urogenital anomalies	32	22	45.2	0
Short stature	18	37	35.3	25

A previously described predisposing factor is the inversion of chromosome 17 in one of the parents, which, while necessary, is not sufficient to produce the microdeletion, as it is a very common polymorphism that is found in up to 20% of the European population.[1] Only two cases of sibling recurrence have been reported in two independent families in which the mothers had a mosaicism for the chromosome 17 deletion, which could be a risk factor for recurrence, underscoring the importance of offering genetic counselling to parents of affected children.[5]

We present a series of four patients with KDVS (Table 1). All patients had some of the clinical features included in the 37 symptoms described by Koolen in the first published series; however, the diagnosis was made when expanded molecular testing was requested following an initial battery of diagnostic tests that were inconclusive. We present a table that summarises what we consider to be the most relevant clinical features described in the most recently published and broader series and those found in our patients (Table 2). Intellectual disability and facial dysmorphism are the most frequently observed features, as was the case in our patients, although potential comorbidities need to be ruled out. Contrary to what has been reported in the literature, none of our patients presented with nephrourologic abnormalities.

Genetic testing in all cases identified mutations in one of the five genes that cause the disease. We ought to highlight the size of the mutation in case 1, which exceeded sizes reported to date.

Recently, the first case has been published of KDVS diagnosed prenatally through the detection of bilateral ventriculomegaly in the pregnancy ultrasound examination performed at 33 weeks' gestation, with confirmation of the microdeletion by means of array-based comparative genomic hybridisation in a sample obtained by amniocentesis.[6] This reinforces the importance of detecting the syndrome early, as it not only allows its aetiological diagnosis, but also genetic counselling for the family. Furthermore, considering that this is a fundamentally monogenic disorder, it is likely that it can benefit from pharmacologic treatment targeting the genome or proteome in the future if research is conducted on this field.

In conclusion, KDVS is a rare disease that must be included in the differential diagnosis of patients with unexplained intellectual disability with or without associated dysmorphic features or malformations. Considering the wide clinical variability that has been observed, we believe that genetic hybridisation techniques must be included at the level of brain MRI in the diagnostic evaluation of these patients.

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