



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Myers, KA;Mandelstam, SA;Ramantani, G;Rushing, EJ;de Vries, BB;Koolen, DA;Scheffer, IE

Title:

The epileptology of Koolen-de Vries syndrome: Electro-clinico-radiologic findings in 31 patients

Date:

2017-06-01

Citation:

Myers, K. A., Mandelstam, S. A., Ramantani, G., Rushing, E. J., de Vries, B. B., Koolen, D. A. & Scheffer, I. E. (2017). The epileptology of Koolen-de Vries syndrome: Electro-clinico-radiologic findings in 31 patients. *Epilepsia*, 58 (6), pp.1085-1094. <https://doi.org/10.1111/epi.13746>.

Persistent Link:

<https://hdl.handle.net/11343/292807>

DR. KENNETH ALEXIS MYERS (Orcid ID : 0000-0001-7831-4593)

DR. GEORGIA RAMANTANI (Orcid ID : 0000-0002-7931-2327)

Received Date : 24-Nov-2016

Revised Date : 08-Mar-2017

Accepted Date : 08-Mar-2017

Article type : Full length original research paper

Author Manuscript

**The Epileptology of Koolen-de Vries Syndrome:  
Electro-clinico-radiologic Findings in 31 Patients**

Running Title: Epileptology of Koolen-de Vries Syndrome

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/epi.13746](https://doi.org/10.1111/epi.13746)

This article is protected by copyright. All rights reserved

Kenneth A. Myers<sup>1,2</sup>, Simone A. Mandelstam<sup>3-5</sup>, Georgia Ramantani<sup>6,7</sup>, Elisabeth J. Rushing<sup>8</sup>,  
Bert B. de Vries<sup>9</sup>, David A. Koolen<sup>9</sup>, Ingrid E. Scheffer<sup>1,3,5,10</sup>

### Affiliations

<sup>1</sup> Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Heidelberg, Victoria, Australia

<sup>2</sup> Alberta Children's Hospital, Cumming School of Medicine, Department of Pediatrics, Section of Neurology, University of Calgary, Calgary, Alberta, Canada

<sup>3</sup> Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia

<sup>4</sup> Department of Radiology, The University of Melbourne, Parkville, Victoria, Australia

<sup>5</sup> The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia

<sup>6</sup> Division of Child Neurology, University Children's Hospital, Zürich, Switzerland

<sup>7</sup> Swiss Epilepsy Center, Zürich, Switzerland

<sup>8</sup> Department of Neuropathology, University Hospital, Zurich, Switzerland

<sup>9</sup> Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands

<sup>10</sup> Department of Neurology, Royal Children's Hospital, Parkville, Victoria, Australia

**Corresponding Author:** Prof. Ingrid Scheffer; Epilepsy Research Centre; Level 2, Melbourne Brain Centre; Austin Health; 245 Burgundy St.; Heidelberg, VIC; 3084;  
[[scheffer@unimelb.edu.au](mailto:scheffer@unimelb.edu.au)], Phone +61-3-9035-7112; Fax +61-3-9496-2291

**Key Words:** Koolen-de Vries syndrome; *KANSLI*; Epilepsy; Brain malformation; Corpus callosum; Periventricular nodular heterotopia

Text Pages: 28; Words: 2614; References: 26; Figures: 2; Tables: 1

## Summary

*Objective:* This study was designed to describe the spectrum of epilepsy phenotypes in Koolen-de Vries syndrome (KdVS), a genetic syndrome involving dysmorphic features, intellectual disability, hypotonia and congenital malformations, that occurs secondary to 17q21.31 microdeletions and heterozygous mutations in *KANSL1*.

*Methods:* We were invited to attend a large gathering of individuals with KdVS and their families. While there, we recruited individuals with KdVS and seizures, and performed thorough phenotyping. Additional subjects were included who approached us after the family support group brought attention to our research via social media. Inclusion criteria were genetic testing results demonstrating 17q21.31 deletion or *KANSL1* mutation, and at least one seizure.

*Results:* Thirty-one individuals were studied, aged 2-35 years. Median age of seizure onset was 3.5 years, and 9/22 had refractory seizures two years after onset. Focal seizures with impaired awareness were the most frequent seizure type occurring in 20/31, usually with prominent autonomic features. Twenty-one patients had prolonged seizures and, at times, refractory status epilepticus. EEG showed focal/multifocal epileptiform discharges in 20/26. MRI studies of 13 patients were reviewed and all had structural anomalies. Corpus callosum dysgenesis, abnormal hippocampi and dilated ventricles were the most common, though periventricular nodular heterotopia, focal cortical dysplasia, abnormal sulcation, brainstem and cerebellum abnormalities were also observed. One patient underwent epilepsy surgery for a lesion that proved to be an angiocentric glioma.

*Significance:* The typical epilepsy phenotype of KdVS involves childhood-onset focal seizures that are prolonged and have prominent autonomic features. Multifocal epileptiform discharges are the typical EEG pattern. Structural brain abnormalities may be universal, including signs of abnormal neuroblast migration and abnormal axonal guidance. Epilepsy surgery should be undertaken with care given the widespread neuroanatomic abnormalities; however, tumors are a rare, yet important, occurrence.

**Key Words:** Koolen-de Vries syndrome; *KANSL1*; Epilepsy; Brain malformation; Corpus callosum; Periventricular nodular heterotopia

**Introduction**

Koolen-de Vries syndrome (KdVS; OMIM #610443) affects multiple organ systems and uniformly involves intellectual disability and characteristic dysmorphic facial features which may include long face, upslanting palpebral fissures, abnormally formed nose, large and prominent ears, everted lower lip, epicanthic folds, and a large and/or broad forehead.<sup>1,2</sup>

Individuals may also have cardiac and renal/urologic malformations, cryptorchidism, skin pigmentation abnormalities and an amiable personality.<sup>1,3</sup> The syndrome was initially described in association with microdeletions at the 17q21.31 locus<sup>4-6</sup> however heterozygous mutations in KAT8 regulatory NSL complex subunit 1 (*KANSL1*), a gene within the common deletion region, can produce the phenotype as well.<sup>7,8</sup> The prevalence of 17q21.31 deletions is estimated to be 0.64% in patients with unexplained mental retardation, however the overall population prevalence of KdVS is unclear.<sup>1</sup>

Phenotyping studies have noted that roughly half of individuals with KdVS have seizures during their lifetime,<sup>1,2,9,10</sup> however the epileptology remains poorly understood. Both focal and generalized seizures have been reported; however, the epilepsy phenotypic spectrum has not been defined.<sup>1,9,11</sup> A typical neuroradiological pattern has not been described although structural brain abnormalities are reported in approximately half, including corpus callosum dysgenesis, enlarged lateral ventricles, abnormal hippocampal shape, Chiari I malformation and subependymal heterotopia.<sup>7,9,10,12,13</sup> In this study, we analysed the epilepsy phenotypes in a cohort of patients with KdVS and seizures, in order to clarify the spectrum of phenotypes that may occur.

## **Methods**

### *Objective*

In this study, we sought to describe the epilepsy phenotype in individuals with KdVS who have experienced seizures, with the goal of characterizing the electro-clinico-radiological presentation, response to treatment, and long term prognosis.

### *Recruitment and Inclusion Criteria*

Subjects were recruited at an international gathering of 62 individuals with KdVS and their families in the United States. Five additional subjects were enrolled after family support groups publicized our research through e-mail lists and social media, leading families of affected individuals in other countries to approach us. Inclusion criteria required that subjects have a confirmed genetic diagnosis of KdVS with either a heterozygous 17q21.31 microdeletion or *KANSL1* mutation.

### *Phenotyping*

In each case, one or more caregivers (usually parents) were interviewed by a pediatric neurologist (KAM for 30 cases and GR for one). Each interview involved a thorough history surrounding seizure patterns and treatment responses, as well as a review of the pregnancy, delivery, developmental, general medical and family histories. A validated seizure questionnaire was used.<sup>14</sup> All available medical records were obtained from the subjects or their medical care teams, including neurology clinic notes and reports from genetic, EEG and neuroimaging

studies. Seizures and epilepsy syndromes were classified according to the International League Against Epilepsy classifications of seizures<sup>15</sup> and epilepsy syndromes.<sup>16,17</sup>

Subjects who were interviewed at least two years following their initial seizure had epilepsy course classified as (A) “early seizure freedom” (seizure-free within six months of starting treatment), (B) “delayed seizure freedom” (seizures not immediately controlled by medication, but became seizure-free at some point after six months), (C) “fluctuating course” (periods of seizure freedom of more than 12 months, interspersed with relapses), or (D) “refractory” (never seizure-free for a continuous 12 month period) following the method defined by Brodie *et al.*<sup>18</sup>

The reports on MRI findings were obtained for 26 cases. For 13 cases, the images on disc were analysed by a pediatric neuroradiologist (SAM).

### *Ethics*

The Human Research Ethics Committee of Austin Health approved the study (Project No. H2007/02961). Written informed consent was obtained from all participants or parents/legal guardians in the case of minors or those with intellectual disability.

### **Results**

From the initial gathering, 26 subjects volunteered to participate in the study, representing 42% (26/62) of attendees. We were only aware of one individual with seizures whose family opted not to participate. Following the gathering, an additional five subjects were enrolled after their families contacted us. Twenty-seven subjects had microdeletions in the 17q21.31 region, with the remaining four having heterozygous mutations of *KANSL1* (c.2725-1G>C, p.(?); c.531\_540del, p.Gly179Leufs\*20; c.2066G>A; p.Trp689\*; c.808\_809delCT; p.Leu270Valfs\*11). The mean age at time of study was 9.8 y (range 2 to 35 y). Genetic details for each subject are in Supporting Information.

Median age of first seizure was 3.5 y (range 4 m to 24 y). Clinical data for each individual are summarized in Table.

### *Seizure Types*

The most common presenting seizure type was focal impaired awareness in 20/31 (65%) subjects. Six subjects also had focal to bilateral tonic-clonic seizures. No definite auras were described. Autonomic signs including pallor, vomiting and oxygen desaturation were frequently reported (14/20). Case 24 had received a diagnosis of Panayiotopoulos syndrome based on this seizure semiology in combination with tonic head deviation. Case 30 had a single seizure with confusion, drooling and unilateral facial clonic movements. Her EEG showed independent, sleep-activated, centrottemporal spikes; consistent with childhood epilepsy with centrottemporal spikes (CECTS).

In addition to the definite focal impaired awareness seizures, non-specific staring spells were reported in 20/31 individuals (65%), usually starting in infancy. Only case 12 had staring spells captured on EEG and confirmed to be seizures (absence with eyelid myoclonias). For the remaining staring spells captured during video-EEG monitoring, reports usually noted no change, though non-diagnostic findings were noted in two patients: generalized decrement in one case and an increase in frequency of interictal discharges in a second. The clinical significance of these staring spells was often unclear, and may have represented a non-epileptic phenomenon in some cases.

Other seizure types were uncommon, but included generalized tonic-clonic without clear focal onset (6/31), drop attacks (2/31), tonic (1/31), absence with eyelid myoclonia (1/31) and infantile spasms (1/31). Seizure type was confirmed via ictal video EEG recording in four patients.

### *Prolonged Seizures and Status Epilepticus*

Twenty subjects (65%) had status epilepticus (seizure > 30 min, seizure > 5 min requiring medication to stop, or multiple seizures within 30 min period without return to baseline status) and an additional child experienced seizures lasting up to 14 minutes that stopped spontaneously. Two subjects had only experienced status in the context of febrile illnesses.

### *Epilepsy Course*

Long term seizure control could be assessed in 22 subjects in whom seizures had begun at least two years prior, based on the Brodie classification system defined in Methods.<sup>18</sup> Of these, nine (41%) had ongoing refractory seizures (D), nine (41%) delayed resolution (B; did not become seizure-free until more than six months after starting treatment), three (14%) immediate resolution (A; seizure-free within six months of starting treatment) and one (5%) a fluctuating course (C; periods of at least 12 months seizure-free, interspersed with relapses).

#### *Response to Specific Medications*

Based on caregiver report, some trends were observed in medication effectiveness. Overall, medications with primarily GABA-ergic mechanisms of action (i.e. benzodiazepines, valproic acid, phenobarbital) were reported as effective, as were the closely related sodium channel inhibitors, carbamazepine and oxcarbazepine. Levetiracetam may have a relative lack of efficacy, only reported to reduce seizure frequency in a minority of cases. A summary of each medication's reported effectiveness is provided in Supporting Information.

#### *EEG*

Of the 26 cases for which EEG reports were available, 20 (77%) showed focal or multifocal epileptiform discharges, often potentiated in sleep. The pattern of focal discharges was variable, though centrottemporal and parietal-occipital discharges were more commonly observed. Background activity was usually normal, though mild focal or generalized background slowing was reported in eight cases, with case 29 having infantile spasms and hypsarrhythmia. Four patients had normal EEG reports. Two cases had generalized epileptiform discharges consisting of spike-wave with frequency 3-4 Hz.

#### *Neuroimaging*

Based on medical records, MRI abnormalities were reported in 15 of 27 subjects (Supporting Information). Of the four remaining patients, one had not had neuroimaging and the remaining three had brain MRI that was reported to be normal by their parents. However, on detailed review by an experienced academic pediatric neuroradiologist of the 13 MRI studies obtained on disc, we found subtle abnormalities present in all subjects. Age at the time of MRI in these cases ranged from 7 days to 21 years.

All patients showed some degree of corpus callosal dysgenesis (Figure 1A-1E). The callosal abnormalities included dysgenesis/absence of the rostrum in 11/13 (85%) and posterior body/splenial abnormalities in 8/13 (62%). Ventriculomegaly with colpocephaly was seen in 11/13 patients (85%), ranging from mild to severe.

Eleven patients (85%) had dysplastic hippocampi, typically involving oval and malrotated morphology with T2 hyperintensity and loss of definition of the internal architecture (Figure 1F-1J). Periventricular nodular heterotopia was identified in 6/13 (46%), five of which involved small, solitary, unilateral frontal or peritrigonal nodules (Figure 2A-2C).

The brainstem morphology was abnormal in 6/13 individuals (46%). Six (46%) had a relatively thick appearance to the medulla (Figure 1A), one a “molar tooth” configuration of the midbrain, one a long flat pons (Figure 1D) and another a short pons. Cerebellar abnormalities were found in 5/13 (38%), including four patients with a bulky cerebellum with large vermis (Figure 1E) and low lying cerebellar tonsils, and one with cerebellar dysplasia.

When olfactory nerves were adequately imaged, they were small in 7/11 patients (64%). An ectopic posterior pituitary was noted in one patient. Case 14 had findings consistent with focal cortical dysplasia, including unusual sulcation with transmantle bands (Figure 2F). Two children had areas of unusual sulcal pattern and three had unilateral Sylvian fissure elongation.<sup>19,20</sup> Case 31 had a T2 hyperintense focal cortical lesion (Figure 2E) resected which was an angiocentric glioma on pathologic analysis (Supporting Information).

Two other patients had neurosurgical intervention based on radiologic abnormalities. Case 20 had a third ventriculostomy for an apparent 3<sup>rd</sup> ventricular arachnoid cyst which was thought to be obstructive and contributing to hydrocephalus (Figure 2D). Case 4 was thought to have obstructive hydrocephalus due to ventricular dilatation and abnormal CSF flow on nuclear medicine study, and subsequently had a ventriculoperitoneal shunt placed.

### *Development*

Developmental impairment or intellectual disability was present in all individuals studied, ranging from mild to severe. Global impairment was considered to be mild or mild-moderate in six patients, moderate in eight, and moderate-severe or severe in the remaining 17. All but two patients (aged 2.5 and 5.9 y) ambulated independently (mean and median age 2.3 y). Expressive language milestones were more delayed, compared to gross and fine motor skills, in 15 individuals (48%) including three who were non-verbal (aged 2.5, 6.7 and 11.5 y). Four patients had diagnoses of autism spectrum disorder, though not all children had undergone formal evaluation. Regression (loss of skills) was reported in 18/31 individuals (58%), often at the same time as seizure onset, but many showed ongoing fluctuation in skills.

### **Discussion**

The epilepsy in KdVS typically presents with early childhood onset focal seizures that are often prolonged and have prominent autonomic features. EEG studies show multifocal discharges which predominate in the posterior quadrants and centrottemporal regions. MRI brain demonstrates a constellation of structural abnormalities with a spectrum of corpus callosal dysgenesis and unusual hippocampal malformation. Seizures can be refractory to initial medical treatments, but are controlled in the long term in more than half. Our findings show that KdVS is associated with focal epilepsy and structural brain malformation. The epilepsy does not fit within a known epilepsy syndrome such as CECTS or Panayiotopoulos syndrome, although there are shared features in some cases.

Although this is not a prospective study of seizures of KdVS, our cohort likely presents a representative picture of the epilepsy spectrum. The family gathering enabled us to study a relatively large population of affected individuals based on their syndromic diagnosis. This approach minimizes selection bias that might occur if individuals were drawn solely from an epilepsy or neurology clinic. Of the total gathering attendees, 42% participated in this seizure-related study, roughly the same percentage that are known to have seizures in KdVS,<sup>1,9,10</sup> thus our cohort should comprise a relatively unbiased, representative sample. However, we cannot exclude a degree of ascertainment bias by virtue of limiting our study to families who elect to participate in family conferences and social media.

When a child with KdVS presents with a first seizure, initial tests should include an EEG and MRI brain, given the high rate of structural abnormalities. Caregivers should be counseled that the range of possible outcomes is broad, but that seizures are likely to be difficult to control in the short term. At two years, over 50% of cases are seizure-free on or off medication.

The observational data in this study suggests patients may have better response to GABAergic anti-epileptic drugs, carbamazepine and oxcarbazepine. Home rescue benzodiazepines should be strongly considered given the high frequency of status epilepticus. Development should be closely monitored as the majority of children will experience regression.

All MRI studies have subtle abnormalities, including nodular heterotopia, that were sometimes missed on the official radiology report. These findings emphasize that neuroradiology studies should be reviewed and reported by experienced neuroradiologists who are aware of the typical abnormalities seen in individuals with KdVS. Despite the unusual hippocampal appearance, these individuals did not have temporal lobe semiology that correlated with the structural findings.

Tumors have not previously been reported in KdVS, emphasizing the importance of case 31 with an angiocentric glioma. This tumor type was first described in 2005,<sup>21,22</sup> and most commonly presents with refractory seizures in childhood. Although angiocentric gliomas are considered low grade tumors, they can transform into, or recur as, more malignant tumors that eventually lead to fatality.<sup>23</sup> Of the 83 published cases of angiocentric glioma, none were associated with a genetic syndrome. In general, gliomas are rarely associated with genetic syndromes; neurofibromatosis 1 and 2, tuberous sclerosis, Turcot syndrome, Li Fraumeni syndrome are the primary genetic syndromes in which there is a clear increased glioma risk.<sup>24</sup> The co-occurrence of angiocentric glioma and KdVS in case 31 is unlikely to be coincidence given the individual rarities of the two diseases, but more study is necessary to determine if there is a significant increased risk of this or other tumor types in KdVS.

There was no clear difference in epilepsy phenotype between individuals with microdeletions and those with *KANSL1* mutations. This comparison was limited by the small number of

individuals with mutations (4), but is nevertheless in line with previous studies that have shown that the specific genomic abnormality does not correlate with overall KdVS phenotype.<sup>10</sup>

Most cases of KdVS are diagnosed in infancy when a comparative genomic hybridization (CGH) microarray is ordered by a pediatrician or clinical geneticist due to dysmorphic features, hypotonia, developmental delay and multisystem abnormalities. However, the non-neurologic abnormalities may be subtle in some cases and a microarray not considered prior to seizure onset.<sup>25</sup> Testing may be considered in cases of Panayiotopoulos syndrome or CECTS, if the patient has developmental delay, dysmorphic features or suggestive MRI findings.

The underlying pathophysiology of epilepsy in KdVS may be complex given the broad role of *KANSL1* in regulation of multiple genes.<sup>26</sup> Neuroblast migration and axonal guidance may both be abnormal, potentially leading to epileptogenic foci such as nodular heterotopia. Epilepsy surgery must be undertaken with caution given that diffuse brain abnormalities are present. An additional consideration is the relatively large proportion of individuals who have spontaneous resolution of seizures following an initial refractory period.

Despite its distinctive dysmorphology, KdVS is not widely recognised by neurologists nor is its epileptology known. Here we show common electro-clinico-radiological features with management implications. As more cases are identified with increasing use of CGH microarray and next generation genetic testing, epilepsy management can be tailored to the syndrome with the use of more efficacious anti-epileptic therapies. Ideally a research trial comparing different treatments may establish the optimal treatment path. Advanced radiologic techniques such as diffusion tensor imaging could be used to investigate the apparently complex pattern of abnormal neuroblast migration and organization. Understanding the clinical phenotype of epilepsy in these patients is crucial in order for neurologists to provide appropriate management and counseling for patients and their families.

### **Acknowledgements**

This study was supported by funding from an Australian National Health and Medical Research Council (NHMRC) Program Grant (628952); I. Scheffer also has a NHMRC Practitioner

Fellowship (1006110). The authors thank the individuals with KdVS and their families for their enthusiastic participation in, and support of, this research project. We also acknowledge the family support groups, Kool Kid Alliance and Supporting Families with Koolen-de Vries Syndrome, who raised awareness of this research.

### **Funding Support and Disclosures**

K. Myers discloses a research grant obtained from the charitable organization Supporting Families with Koolen-de Vries Syndrome, being used to conduct a follow up study. I. Scheffer discloses payments from UCB Pharma, Athena Diagnostics, and Transgenomics for lectures and educational presentations. The remaining authors have no conflicts of interest.

**Ethical Publication Statement:** We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### **Figure Legends**

Figure 1 – Typical Neuroradiologic Phenotype of Individuals with Koolen-de Vries Syndrome and Seizures. The range of corpus callosum dysgenesis is demonstrated in A-E (Cases 3, 30, 9, 11, 20). Foreshortened corpus callosum with small clubbed splenium shown in A. Foreshortened corpus callosum is also seen in B. C and E demonstrate absence of posterior body and splenium. Absent rostrum, clubbed genu, short and irregular posterior bodies and rudimentary splenium are seen in D. Dysplastic brainstem features are also noted in A, with thickened medulla and absence of normal pontomedullary junction, and D with thickened and elongated pons. Bulky cerebellum with large vermis is also apparent in E. Typical hippocampal malformations are shown in F-J (Cases 3, 31, 9, 11, 20). Hippocampi are generally oval shaped, malrotated and show T2 hyperintensity and loss of normal internal architecture.

Figure 2 – Periventricular Nodular Heterotopia and Other Less Common Neuroimaging Abnormalities in Koolen-de Vries Syndrome. Periventricular nodular heterotopia is shown in A-C (cases 14, 20, 19). A cystic lesion occupying the 3<sup>rd</sup> ventricle and compressing and displacing the mammillary bodies is seen in D (case 20). Focal T2 hyperintense lesion in the right frontal region is seen in E, diagnosed as an angiocentric glioma on pathology (case 31). F shows a focal

region of abnormal sulcation with transmantle bands, consistent with a focal cortical dysplasia (case 19).

**Table: Epilepsy and Developmental Features.** Medications were classified as “effective” if caregivers reported at least partial improvement in seizure control, and “ineffective” if there was no apparent improvement. Refer to Methods for definitions of Brodie class (A), (B), (C) and (D). “Prolonged seizure” is defined as > 10 min or rescue medication given after 5 min to stop. “?” denotes parents could not recall the timing of the milestone.

#/ Sex/ Age (y)/ Del or Mut	Sz ons et (y)	Sz Typ es (pre senti ng type in bold )	Seizure Triggers	Aut ono mic feat ures ?	Pr olo ng ed sz?	EEG	Epilepsy Course (Brodie class)	Effect ive Meds	Ineffecti ve Meds	Developme ntal Milestones (sat/walked /first word) Severity of Intellectual Disability (Estimated)
1/F/ 4/De l	1.5	<b>T</b>	None.	N	N	Left and right frontal/cen tral sharp waves.	(A) Sz free on medicatio n.	PB	-	8 m/19 m/3 y Mild- Moderate
2/M/ 11/D el	3	<b>F- EG, DA,</b>	Stress, fever.	N	Y	N/A	(B) Sz free off medicatio	VPA	LEV	8 m/16 m/18 m Mild

		SS					n since 7 y of age.			
3/M/ 11/D el	5	F- IA, SS	Illness, fear/anxi ety, dehydrati on, fatigue, temperat ure change	Y	Y	Left temporal sharp and SW.	(D) Incomplet e sz control.	LEV	-	3 y/4 y/NV Severe
4/F/ 21/D el	2	GT C, SS	Sleep.	N	Y	Normal.	(B) Sz free off medicatio n since 9 y of age.	CLN	KD	12 m/2.5 y/2.5 y Mild- Moderate
5/F/ 9/M ut	5	F- EG, F- IA, SS	Sleep deprivati on, stress.	Y	Y	Left posterior SW and slowing initially, later multifocal SW and generalize d slowing. Sz have occipital onset.	(D) Refractory	OXC, VPA, CLN	LEV	2 y/3 y/5 y Severe
6/F/ 7/M	5	F- IA,	Sleep.	Y	Y	Multifocal SW, PSW	Refractory .	ZNS, OXC	LEV	12 m/3 y/5 y

ut		SS, DA				and slowing (mainly left posterior).				Moderate- Severe
7/F/ 9/De 1	1.5	<b>GT</b> C, A, F- IA, SS	None.	N	Y	Multifocal sharps, left posterior and right frontocent ral. Focal ESES.	(D) Refractory	CLB	CBZ, LEV, LTG, TPM	11 m/2.5 y/2 y Moderate
8/F/ 5/De 1	2	<b>FS</b> (F- IA)	Fever and viral illnesses.	N	Y	N/A	(B) Resolved spontaneo usly.	-	LEV	16 m/28 m/3 y Moderate
9/F/ 2/De 1	0.3	<b>GT</b> C, F- IA, SS	Viral illnesses.	N	Y	Sharps synchrono us and asynchron ous in frontal regions.	Sz controlled on ZNS.	ZNS, LEV	-	18 m/NW/NV Severe
10/F /9/D el	0.8	<b>FS</b> (HC ) HC, abse nce with eyeli	Fever, sleep.	N	N	Multifocal spikes, predomina ntly right central. Continuou s focal and generalize	(D) Sz controlled on medicatio n, but ESES refractory.	LEV, CLB, VPA	-	9 m/2 y/2 y Moderate

		d myo cloni a				d SW during sleep (ESES). Absence sz with eyelid myoclonia .				
11/ M/7/ Del	2	<b>F- IA, SS</b>	Sleep.	Y	Y	Multifocal sharps, activated in sleep.	(C) Rare sz on LEV.	LEV	-	11 m/18 m/4.5 y Moderate- Severe
12/F /35/ Del	25	<b>GT C</b>	None.	N	N	Left posterior slowing, sharps and spikes.	(A) Only one definite event.	LTG	-	?/2.5 y/? Moderate- Severe
13/F /2/D el	0.5	<b>F- IA, SS</b>	Viral illnesses.	N	Y	Normal.	Sz free on medicatio n.	TPM	LEV	10 m/20 m/13 m Mild- Moderate
14/ M/6/ Del	6	<b>GT C, SS</b>	None.	N	N	3-4 Hz generalize d SW.	Only one definite event.	VPA	-	9 m/13 m/NV Moderate
15/ M/8/ Del	8	<b>GT C, SS</b>	None.	Y	N	N/A	Only one definite event.	LEV	-	6 m/12 m/3.8 y Moderate
16/ M/8/ Del	2	<b>F- IA, HC,</b>	Sleep.	Y	Y	Multifocal epileptifor m	(D) Refractory .	LEV, LTG, OXC,	-	15 m/3 y/18 m Moderate-

		SS				discharges (central- parietal).		CBZ, TPM, VPA		Severe
17/F /7/D el	4	<b>F- IA, F- EG</b>	None.	Y	Y	Mild backgroun d slowing and focal spikes in left Rolandic region.	(C) Sz free with addition of PHT.	CBZ, DZP, PHT	-	10 m/2 y/4 y Moderate- Severe
18/F /16/ Del	1	<b>GT C</b>	None.	N	Y	N/A	(A) Only one event. Sz free off medicatio n.	CBZ	-	7 m/13 m/Unclear Mild- Moderate
19/F /8/D el	4	SS	None.	N	N	Right centrotem poral spikes and sharps, potentiate d in sleep. Mild backgroun d slowing	Medicatio n not started. Sz q3-6 mths.	-	-	12 m/18 m/4 y Moderate
20/F /5/D el	2	<b>GT C, SS</b>	Viral illnesses.	Y	Y	Normal.	(D) Sz free on medicatio n.	CLN	LEV, LTG	12 m/NW/18 m Moderate-

										Severe
21/ M/2 2/De 1	0.8	<b>FS,</b> <b>SS</b>	Viral illnesses, fever.	N	Y	N/A	(B) Sz free off medicatio n.	PB	CBZ	12 m/3 y/6 y Moderate- Severe
22/F /11/ Mut	6	<b>F- IA,</b> <b>HC,</b> <b>SS</b>	Illness, sleep.	Y	Y	Focal slowing, spikes and SW from right posterior region.	(B) Sz free on medicatio n.	CBZ	-	11 m/2.5 y/2.5 y Moderate
23/ M/1 0/De 1	4	<b>F- IA</b>	None.	N	N	Bilateral independe nt sharp and SW.	(B) Sz free on medicatio n.	CBZ	LTG	3 y/4 y/4 y Severe
24/ M/2 1/De 1	17	<b>F- IA</b>	None.	Y	N	Normal.	Sz free on medicatio n.	LEV	-	18 m/4 y/3 y Moderate- Severe
25/ M/1 7/De 1	4	<b>F- IA,</b> <b>F- EG</b>	None.	N	Y	Backgroun d slowing. Left centrotem poral sharps.	(B) Sz free on medicatio n.	TPM, VPA, OXC	LEV	7.5 m/18 m/2 y Moderate- Severe
26/F /6/D el	5	<b>SS</b>	None.	-	N	Multifocal sharp-slow and SW, mainly central,	Started on VPA based on EEG; no definite	-	-	8 m/22 m/3 y Moderate

						temporal and parietal.	clinical events.			
27/F /11/ Del	3	SS, F-IA	Dehydration, illness, sleep.	Y	Y	Right centrotemporal SW	(B) Rare sz on medication.	VPA, CBZ	-	7 m/21 m/14 m Mild
28/F /4/D el	4	F- IA	None.	Y	Y	Frequent centrotemporal epileptiform discharges, activated in sleep. Consistent with BECTS.	Only one event.	-	-	9 m/34 m/17 m Moderate- Severe
29/F /3/D el #	0.3	IS	None.	N	N	Hypsarrhythmia w/ IS.	(B) Spasms resolved at ~13 m. Sz free off medication.	ACT H, KD, TPM	-	18 m/2.7 y/4 y Severe
30/F /3/M ut	2	F- IA, SS	Illness and fever.	Y	Y	Mild background slowing.	Sz free on medication.	OXC	-	11 m/2.8 y/18 m Moderate
31/F /4/D el	3	F- IA (FS	Fever.	Y	Y	Right frontal spikes,	Sz free on medication.	TPM, LTG	LEV	14 m/25 m/4 y Severe

		<b>HC)</b>			polyspikes and sharp waves. Right frontal slowing and fast activity. Subclonica l sz originating at F4.				
--	--	------------	--	--	--	--	--	--	--

Abbreviations: A (Absence seizure); ACTH (Adrenocorticotrophic hormone); CBZ (Carbamazepine); CECTS (Benign epilepsy with centrotemporal spikes); CLB (Clobazam); CLN (Clonazepam); DA (Drop attacks not better delineated); DZP (Diazepam); EEG (Electroencephalography); ESES (Electrical status epilepticus in sleep); F-EG (Focal seizure with evolution to generalized tonic-clonic); F-IA (Focal seizures with impaired awareness); FS (Febrile seizures); GTC (Generalized tonic-clonic seizure); HC (Hemiclonic); IS (Infantile spasms); KD (Ketogenic diet); LEV (Levetiracetam); LTG (Lamotrigine); N/A (Not available); NV (Non-verbal); NW (Not walking); OXC (Oxcarbazepine); PB (Phenobarbital); PHT (Phenytoin); PSW (Polyspike-wave); Sz (Seizure); SS (Staring spells not better delineated); SW (Spike-wave); T (Tonic seizure); TPM (Topiramate); VPA (Valproate); ZNS (Zonisamide).

# Patient 29 published previously.<sup>11</sup>

### **Key Points**

- Seizures in Koolen-de Vries syndrome are usually focal, and are frequently prolonged with prominent autonomic features.
- EEG typically shows focal and multifocal epileptiform discharges.
- The common pattern of brain malformation comprises corpus callosum dysgenesis and hippocampal malformation.
- Ventricular dilatation, periventricular nodular heterotopia and olfactory nerve hypoplasia are also frequently observed.
- 9/22 patients (41%) had refractory seizures two years after onset.

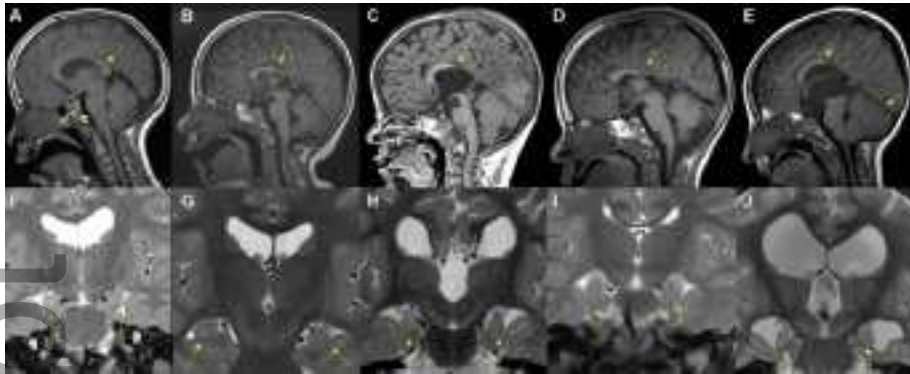
### **References**

1. Koolen DA, Sharp AJ, Hurst JA, et al. Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. *J Med Genet* 2008;45:710-720.
2. Tan TY, Aftimos S, Worgan L, et al. Phenotypic expansion and further characterisation of the 17q21.31 microdeletion syndrome. *J Med Genet* 2009;46:480-489.
3. Maley AM, Spraker MK, de Vries BB, et al. Vitiligo in the Koolen-de Vries or 17q21.31 microdeletion syndrome. *Clin Dysmorphol* 2015;24:86-87.
4. Sharp AJ, Hansen S, Selzer RR, et al. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. *Nat Genet* 2006;38:1038-1042.
5. Koolen DA, Vissers LE, Pfundt R, et al. A new chromosome 17q21.31 microdeletion syndrome associated with a common inversion polymorphism. *Nat Genet* 2006;38:999-1001.
6. Shaw-Smith C, Pittman AM, Willatt L, et al. Microdeletion encompassing MAPT at chromosome 17q21.3 is associated with developmental delay and learning disability. *Nat Genet* 2006;38:1032-1037.
7. Koolen DA, Kramer JM, Neveling K, et al. Mutations in the chromatin modifier gene KANSL1 cause the 17q21.31 microdeletion syndrome. *Nat Genet* 2012;44:639-641.
8. Zollino M, Orteschi D, Murdolo M, et al. Mutations in KANSL1 cause the 17q21.31 microdeletion syndrome phenotype. *Nat Genet* 2012;44:636-638.
9. Zollino M, Marangi G, Ponzi E, et al. Intragenic KANSL1 mutations and chromosome 17q21.31 deletions: broadening the clinical spectrum and genotype-phenotype correlations in a large cohort of patients. *J Med Genet* 2015;52:804-814.
10. Koolen DA, Pfundt R, Linda K, et al. The Koolen-de Vries syndrome: a phenotypic comparison of patients with a 17q21.31 microdeletion versus a KANSL1 sequence variant. *Eur J Hum Genet* 2016;24:652-659.
11. Wray CD. 17q21.31 microdeletion associated with infantile spasms. *Eur J Med Genet* 2013;56:59-61.
12. Dubourg C, Sanlaville D, Doco-Fenzy M, et al. Clinical and molecular characterization of 17q21.31 microdeletion syndrome in 14 French patients with mental retardation. *Eur J Med Genet* 2011;54:144-151.

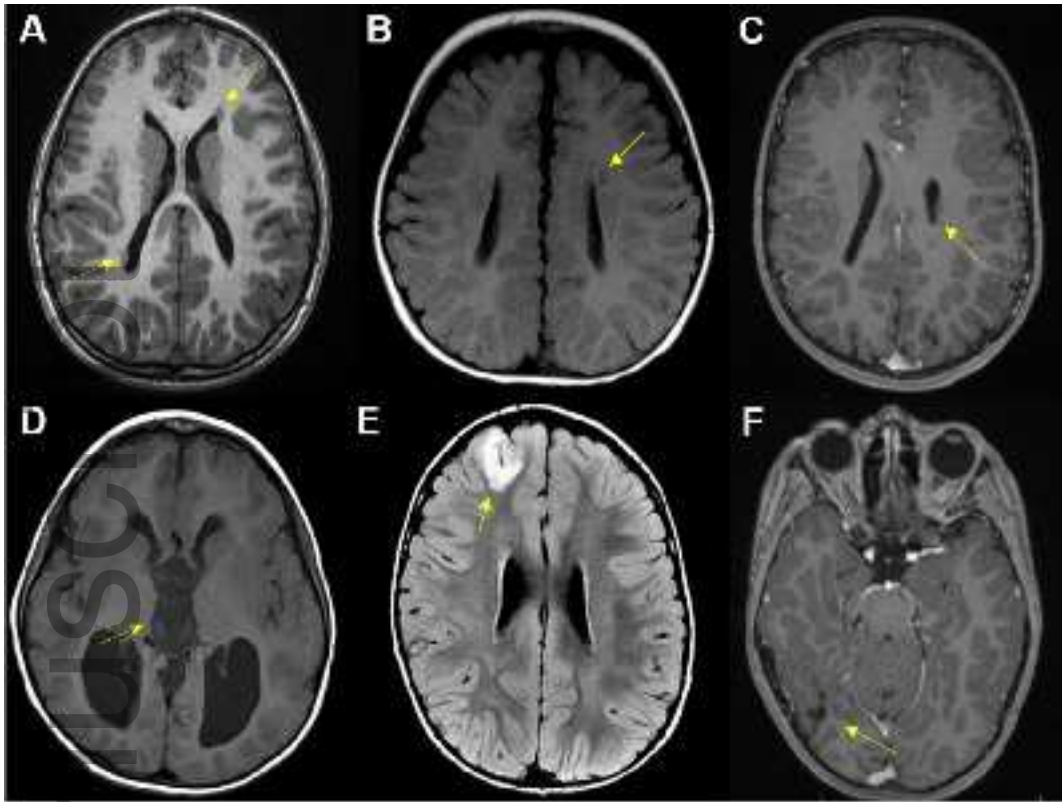
13. Terrone G, D'Amico A, Imperati F, et al. A further contribution to the delineation of the 17q21.31 microdeletion syndrome: central nervous involvement in two Italian patients. *Eur J Med Genet* 2012;55:466-471.
14. Reutens DC, Howell RA, Gebert KE, et al. Validation of a questionnaire for clinical seizure diagnosis. *Epilepsia* 1992;33:1065-1071.
15. Proposal for classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1985;26:268-278.
16. ILAE CoCaT. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;30:389-399.
17. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-685.
18. Brodie MJ, Barry SJ, Bamagous GA, et al. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;78:1548-1554.
19. Guibaud L, Salleret L, Larroche JC, et al. Abnormal Sylvian fissure on prenatal cerebral imaging: significance and correlation with neuropathological and postnatal data. *Ultrasound Obstet Gynecol* 2008;32:50-60.
20. Sarnat HB, Flores-Sarnat L. Telencephalic Flexure and Malformations of the Lateral Cerebral (Sylvian) Fissure. *Pediatr Neurol* 2016;63:23-38.
21. Wang M, Tihan T, Rojiani AM, et al. Monomorphous angiocentric glioma: a distinctive epileptogenic neoplasm with features of infiltrating astrocytoma and ependymoma. *J Neuropathol Exp Neurol* 2005;64:875-881.
22. Lellouch-Tubiana A, Boddaert N, Bourgeois M, et al. Angiocentric neuroepithelial tumor (ANET): a new epilepsy-related clinicopathological entity with distinctive MRI. *Brain Pathol* 2005;15:281-286.
23. McCracken JA, Gonzales MF, Phal PM, et al. Angiocentric glioma transformed into anaplastic ependymoma: Review of the evidence for malignant potential. *J Clin Neurosci* 2016;34:47-52.

24. Johansson G, Andersson U, Melin B. Recent developments in brain tumor predisposing syndromes. *Acta Oncol* 2016;55:401-411.
25. Bernardo P, Madia F, Santulli L, et al. 17q21.31 microdeletion syndrome: Description of a case further contributing to the delineation of Koolen-de Vries syndrome. *Brain Dev* 2016;
26. Li X, Wu L, Corsa CA, et al. Two mammalian MOF complexes regulate transcription activation by distinct mechanisms. *Mol Cell* 2009;36:290-301.

Author Manuscript



epi\_13746\_f1.tif



epi\_13746\_f2.tif

Author Manuscript