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FULL-LENGTH ORIGINAL RESEARCH

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

*†Kenneth A. Myers, ‡§¶Simone A. Mandelstam, #**Georgia Ramantani, ††Elisabeth J. Rushing, ‡‡Bert B. de Vries, ‡‡David A. Koolen, and *‡¶§§Ingrid E. Scheffer

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Kenneth A. Myers, pediatric neurologist and epilepsy fellow at Austin Health, University of Melbourne

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 at seizure onset was 3.5 years, and 9 of 22 had refractory seizures 2 years after onset. Focal impaired awareness seizures were the most frequent seizure type occurring in 20 of 31, usually with prominent autonomic features. Twenty-one patients had prolonged seizures and, at times, refractory status epilepticus. Electroencephalography (EEG) showed focal/multifocal epileptiform discharges in 20 of 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, although periventricular nodular heterotopia, focal cortical dysplasia, abnormal sulcation, and 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.**

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*Department of Medicine, Epilepsy Research Centre, The University of Melbourne, Austin Health, Heidelberg, Victoria, Australia; †Section of Neurology, Department of Pediatrics, Alberta Children's Hospital, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; ‡Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia; §Department of Radiology, The University of Melbourne, Parkville, Victoria, Australia; ¶The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia; #Division of Child Neurology, University Children's Hospital, Zurich, Switzerland; **Swiss Epilepsy Center, Zurich, Switzerland; ††Department of Neuropathology, University Hospital, Zurich, Switzerland; ‡‡Department of Human Genetics, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands; and §§Department of Neurology, Royal Children's Hospital, Parkville, Victoria, Australia

Address correspondence to Ingrid E. Scheffer, Epilepsy Research Centre, Level 2, Melbourne Brain Centre, Austin Health, 245 Burgundy St., Heidelberg, Vic. 3084, Australia. E-mail: scheffer@unimelb.edu.au

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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 dilation, periventricular nodular heterotopia, and olfactory nerve hypoplasia are also frequently observed
- Nine (41%) of 22 patients had refractory seizures 2 years after onset

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.[1,2] In addition, individuals may also have cardiac and renal/urologic malformations, cryptorchidism, skin-pigmentation abnormalities, and an amiable personality.[1,3] The syndrome was initially described in association with microdeletions at the 17q21.31 locus[4–6]; however, heterozygous mutations in KAT8 regulatory nonspecific lethal complex subunit 1 (*KANSL1*), a gene within the common deletion region, can produce the phenotype as well.[7,8] 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.[1]

Phenotyping studies have noted that roughly half of individuals with KdVS have seizures during their lifetime[1,2,9,10]; however, the epileptology remains poorly understood. Although both focal and generalized seizures have been reported, the epilepsy phenotypic spectrum has not been defined.[1,9,11] A typical neuroradiologic 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.[7,9,10,12,13] In this study, we analyzed 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-radiologic 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.[14] All available medical records were obtained from the subjects or their medical care teams, including neurology clinic notes and reports from genetic, electroencephalography (EEG) and neuroimaging studies. Seizures and epilepsy syndromes were classified according to the International League Against Epilepsy (ILAE) classifications of seizures[15] and epilepsy syndromes.[16,17]

Subjects who were interviewed at least 2 years following their initial seizure had epilepsy course classified as (A) "early seizure freedom" (seizure-free within 6 months of starting treatment), (B) "delayed seizure freedom" (seizures not immediately controlled by medication, but became seizure-free at some point after 6 months), (C) "fluctuating course" (periods of seizure freedom of >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.[18]

The reports on magnetic resonance imaging (MRI) findings were obtained for 26 cases. For 13 cases, the images on disc were analyzed 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 aware of only 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 the time of the study was 9.8 years (range 2–35 years). Genetic details for each subject are in Table S1.

Median age at first seizure was 3.5 years (range 4 months to 24 years). Clinical data for each individual are summarized in Table 1.

Seizure types

The most common presenting seizure type was focal impaired awareness in 20 (65%) of 31 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, centrotemporal spikes consistent with childhood epilepsy with centrotemporal spikes (CECTS).

In addition to the definite focal impaired awareness seizures, nonspecific staring spells were reported in 20 (65%) of 31 individuals, 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, although nondiagnostic 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 nonepileptic 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 a 30-min period without return to baseline status), and an additional child experienced seizures lasting up to 14 min 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 2 years prior, based on the Brodie classification system defined in Methods.[18] Of these, nine (41%) had ongoing refractory seizures (D), nine (41%) had delayed resolution (B; did not become seizure-free until > 6 months after starting treatment), three (14%) had immediate resolution (A; seizure-free within 6 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 γ-aminobutyric acid (GABA) agonist mechanisms of action (i.e., benzodiazepines, valproic acid, and 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 Table S2.

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, although centrotemporal and parietooccipital discharges were more commonly observed. Background activity was usually normal, although 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 (Table S3). Of the four remaining patients, one had not had neuroimaging and the remaining three had brain magnetic resonance imaging (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 disk, 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 (Fig. 1A–E). The callosal abnormalities included dysgenesis/absence of the rostrum in 11 (85%) of 13 and posterior body/splenial abnormalities in 8 (62%) of 13. Ventriculomegaly with colpocephaly was seen in 11 (85%) of 13 patients, ranging from mild to severe.

Eleven patients (85%) had dysplastic hippocampi, typically involving oval and malrotated morphology with T_2

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Table 1. Epilepsy and developmental features

No./sex/ age (y)/ del or mut	Sz onset (y)	Sz types (presenting type in bold)	Seizure triggers	Autonomic features?	Prolonged sz?	EEG	Epilepsy course (Brodie class)	Effective meds	Ineffective meds	Developmental milestones (sat/walked/first word) severity of intellectual disability (estimated)
1/F/4/del	1.5	**T**	None	N	N	Left and right frontal/central sharp waves	(A) Sz-free on medication	PB	–	8 months /19 months/3 years Mild-moderate
2/M/11/del	3	**F-EG**, DA, SS	Stress, fever	N	Y	N/A	(B) Sz-free off medication since 7 years of age	VPA	LEV	8 months/16 months/18 months Mild
3/M/11/del	5	**F-IA**, SS	Illness, fear/anxiety, dehydration, fatigue, temperature change	Y	Y	Left temporal sharp and SW	(D) Incomplete sz control	LEV	–	3 years/4 years/NV Severe
4/F/ 21/del	2	**GTC**, SS	Sleep	N	Y	Normal	(B) Sz-free off medication since 9 years of age	CLN	KD	12 months/2.5 years/2.5 years Mild-moderate
5/F/9/mut	5	**F-EG**, F-IA, SS	Sleep deprivation, stress	Y	Y	Left posterior SW and slowing initially, later multifocal SW and generalized slowing. Sz have occipital onset	(D) Refractory	OXC, VPA, CLN	LEV	2 years/3 years/5 years Severe
6/F/7/mut	5	**F-IA**, SS, DA	Sleep	Y	Y	Multifocal SW, PSW and slowing (mainly left posterior)	Refractory	ZNS, OXC	LEV	12 months/3 years/5 years Moderate-severe
7/F/9/del	1.5	**GTC**, A, F-IA, SS	None	N	Y	Multifocal sharps, left posterior and right frontocentral Focal ESES	(D) Refractory	CLB	CBZ, LEV, LTG, TPM	11 months/2.5 years/2 years Moderate
8/F/5/del	2	**FS (F-IA)**	Fever and viral illnesses	N	Y	N/A	(B) Resolved spontaneously	–	LEV	16 months/28 months/3 years Moderate
9/F/2/del	0.3	**GTC**, F-IA, SS	Viral illnesses	N	Y	Sharps synchronous and asynchronous in frontal regions	Sz controlled on ZNS	ZNS, LEV	–	18 months/NW/NV Severe

Continued

Table 1. Continued.

No./sex/ age (y)/ del or mut	Sz onset (y)	Sz types (presenting type in bold)	Seizure triggers	Autonomic features?	Prolonged sz?	EEG	Epilepsy course (Brodie class)	Effective meds	Ineffective meds	Developmental milestones (sat/walked/first word) severity of intellectual disability (estimated)
10/F/9/del	0.8	**FS (HC)**, HC, absence with eyelid myoclonia	Fever, sleep	N	N	Multifocal spikes, predominantly right central. Continuous focal and generalized SW during sleep (ESES). Absence sz with eyelid myoclonia	(D) Sz controlled on medication, but ESES refractory	LEV, CLB, VPA	–	9 months/2 years/2 years Moderate
11/M/7/del	2	**F-IA**, SS	Sleep	Y	Y	Multifocal sharps, activated in sleep	(C) Rare sz on LEV	LEV	–	11 months/18 months/4.5 years Moderate-severe
12/F/35/del	25	**GTC**	None	N	N	Left posterior slowing, sharps and spikes	(A) Only one definite event	LTG	–	?/2.5 years/? Moderate-severe
13/F/2/del	0.5	**F-IA**, SS	Viral illnesses	N	Y	Normal	Sz-free on medication	TPM	LEV	10 months/20 months/13 months Mild-Moderate
14/M/6/del	6	**GTC**, SS	None	N	N	3–4 Hz generalized SW	Only one definite event	VPA	–	9 months/13 months/NV Moderate
15/M/8/del	8	**GTC**, SS	None	Y	N	N/A	Only one definite event	LEV	–	6 months/12 months/3.8 years Moderate
16/M/8/del	2	**F-IA**, HC, SS	Sleep	Y	Y	Multifocal epileptiform discharges (central-parietal)	(D) Refractory	LEV, LTG, OXC, CBZ, TPM, VPA	–	15 months/3 years/18 months Moderate-severe
17/F/7/del	4	**F-IA**, F-EG	None	Y	Y	Mild background slowing and focal spikes in left Rolandic region	(C) Sz-free with addition of PHT	CBZ, DZP, PHT	–	10 months /2 years/4 years Moderate-severe
18/F/16/del	1	**GTC**	None	N	Y	N/A	(A) Only one event. Sz-free off medication	CBZ	–	7 months/13 months/unclear Mild-moderate
19/F/8/del	4	**SS**	None	N	N	Right centrotemporal spikes and sharps, potentiated in sleep. Mild background slowing	Medication not started. Sz q3-6 mo	–	–	12 months/18 months /4 years Moderate

Continued

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Table 1. Continued.

No./sex/ age (y)/ del or mut	Sz onset (y)	Sz types (presenting type in bold)	Seizure triggers	Autonomic features?	Prolonged sz?	EEG	Epilepsy course (Brodie class)	Effective meds	Ineffective meds	Developmental milestones (sat/walked/first word) severity of intellectual disability (estimated)
20/F/5/del	2	**GTC**, SS	Viral illnesses	Y	Y	Normal	(D) Sz-free on medication	CLN	LEV, LTG	12 months /NW/18 months Moderate-Severe
21/M/22/del	0.8	**FS**, SS	Viral illnesses, fever	N	Y	N/A	(B) Sz-free off medication	PB	CBZ	12 months/3 years/6 years Moderate-Severe
22/F/11/mut	6	**F-IA**, HC, SS	Illness, sleep	Y	Y	Focal slowing, spikes and SW from right posterior region	(B) Sz-free on medication	CBZ	–	11 months/2.5 years/2.5 years Moderate
23/M/10/del	4	**F-IA**	None	N	N	Bilateral independent sharp and SW	(B) Sz-free on medication	CBZ	LTG	3 years/4 years/4 years Severe
24/M/21/del	17	**F-IA**	None	Y	N	Normal	Sz-free on medication	LEV	–	18 months/4 years/3 years Moderate-severe
25/M/17/del	4	**F-IA**, F-EG	None	N	Y	Background slowing. Left centrotemporal sharps	(B) Sz-free on medication	TPM, VPA, OXC	LEV	7.5 months/18 months/2 years Moderate-severe
26/F/6/del	5	**SS**	None	–	N	Multifocal sharp-slow and SW, mainly central, temporal and parietal	Started on VPA based on EEG; no definite clinical events	–	–	8 months/22 months/3 years Moderate
27/F/11/del	3	**SS**, F-IA	Dehydration, illness, sleep	Y	Y	Right centrotemporal SW	(B) Rare sz on medication	VPA, CBZ	–	7 months/21 months/14 months Mild
28/F/4/del	4	**F-IA**	None	Y	Y	Frequent centrotemporal epileptiform discharges, activated in sleep. Consistent with BECTS	Only one event	–	–	9 months/34 months/17 months Moderate-severe
29/F/3/del [a]	0.3	**IS**	None	N	N	Hypsarrhythmia w/ IS	(B) Spasms resolved at ~13 months. Sz-free off medication	ACTH, KD, TPM	–	18 months/2.7 years/4 years Severe
30/F/3/mut	2	**F-IA**, SS	Illness and fever	Y	Y	Mild background slowing	Sz-free on medication	OXC	–	11 months/2.8 years /18 months Moderate

Continued

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Table 1. Continued.

No./sex/ age (y)/ del or mut	Sz onset (y)	Sz types (presenting type in bold)	Seizure triggers	Autonomic features?	Prolonged sz?	EEG	Epilepsy course (Brodie class)	Effective meds	Ineffective meds	Developmental milestones (sat/walked/first word) severity of intellectual disability (estimated)
31/F/4del	3	**F-IA (FS HC)**	Fever	Y	Y	Right frontal spikes, polyspikes and sharp waves. Right frontal slowing and fast activity. Subclinical sz originating at F4	Sz-free on medication	TPM, LTG	LEV	14 months/25 months/4 years Severe

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.

A, absence seizure; ACTH, adrenocorticotrophic hormone; CBZ, carbamazepine; CECTS, childhood 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 impaired awareness seizures; 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, nonverbal; 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.

[a]Patient 29 published previously.[11]

hyperintensity and loss of definition of the internal architecture (Fig. 1F–J). Periventricular nodular heterotopia was identified in 6 (46%) of 13 patients, 5 of which involved small, solitary, unilateral frontal or peritrigonal nodules (Fig. 2A–C).

The brainstem morphology was abnormal in 6 (46%) of 13 individuals. Six patients (46%) had a relatively thick appearance to the medulla (Fig. 1A), one a "molar tooth" configuration of the midbrain, one a long flat pons (Fig. 1D), and another a short pons. Cerebellar abnormalities were found in 5 (38%) of 13, including 4 patients with a bulky cerebellum with large vermis (Fig. 1E) and low lying cerebellar tonsils, and one with cerebellar dysplasia.

When olfactory nerves were adequately imaged, they were small in 7 (64%) of 11 patients. An ectopic posterior pituitary was noted in one patient. Case 14 had findings consistent with focal cortical dysplasia, including unusual sulcation with transmantle bands (Fig. 2F). Two children had areas of unusual sulcal pattern and three had unilateral Sylvian fissure elongation.[19,20] Case 31 had a T_2 hyperintense focal cortical lesion (Fig. 2E) resected, which was an angiocentric glioma on pathologic analysis (Figure S1).

Two other patients had neurosurgical intervention based on radiologic abnormalities. Case 20 had a third ventriculostomy for an apparent third ventricular arachnoid cyst, which was thought to be obstructive and contributing to hydrocephalus (Fig. 2D). Case 4 was thought to have obstructive hydrocephalus due to ventricular dilation and abnormal cerebrospinal fluid (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 mild or mild–moderate in 6 patients, moderate in 8, and moderate–severe or severe in the remaining 17. All but two patients (aged 2.5 and 5.9 years) ambulated independently (mean and median age 2.3 years). Expressive language milestones were more delayed, compared to gross and fine motor skills, in 15 individuals (48%) including 3 who were nonverbal (aged 2.5, 6.7, and 11.5 years). Four patients had diagnoses of autism spectrum disorder, although not all children had undergone formal evaluation. Regression (loss of skills) was reported in 18 (58%) of 31 individuals, 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 that predominate in the posterior quadrants and centrotemporal regions. MRI brain demonstrates a constellation of structural abnormalities with a spectrum of

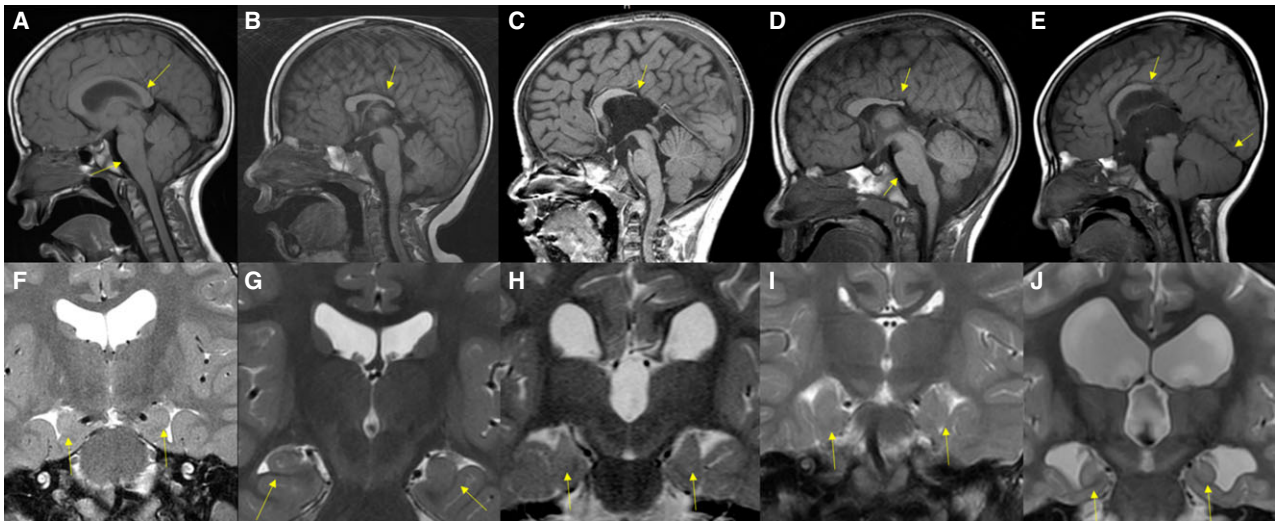

Figure 1.
Typical neuroradiologic phenotype of individuals with Koolen-de Vries syndrome and seizures. The range of corpus callosum dysgenesis is demonstrated in (**A**–**E**) (Cases 3, 30, 9, 11, and 20). Foreshortened corpus callosum with small clubbed splenium shown in (**A**). Foreshortened corpus 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, and 20). Hippocampi are generally oval shaped, malrotated, and show T_2 hyperintensity and loss of normal internal architecture.

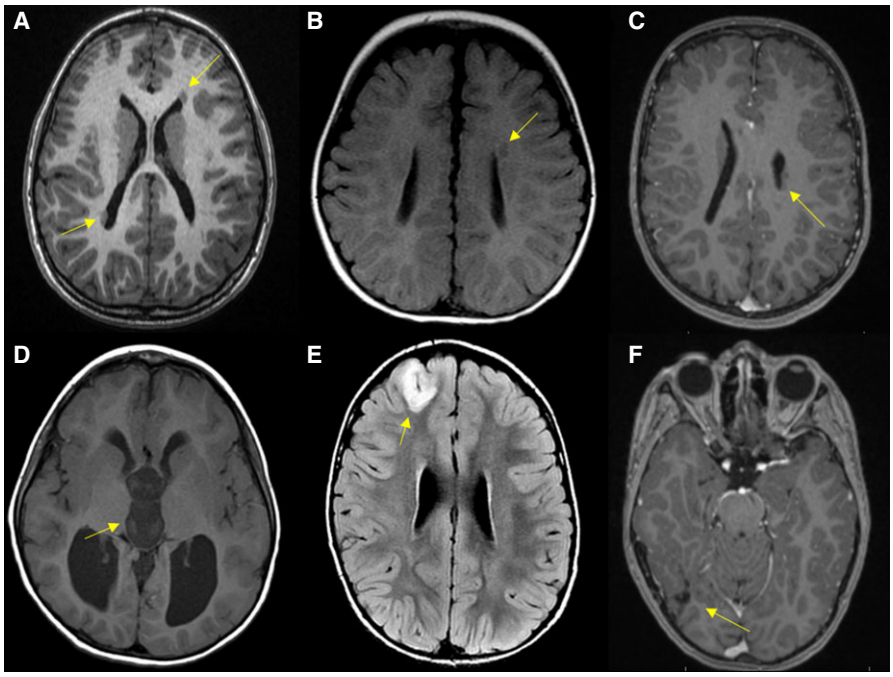

Figure 2.
Periventricular nodular heterotopia and other less common neuroimaging abnormalities in Koolen-de Vries syndrome. Periventricular nodular heterotopia is shown in (**A**–**C**) (cases 14, 20, and 19). A cystic lesion occupying the third ventricle and compressing and displacing the mammillary bodies is seen in (**D**) (case 20). Focal T_2 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).

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[1,9,10]; therefore, our cohort should comprise a relatively unbiased, representative sample. However, we cannot exclude a degree of ascertainment bias related to 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 EEG and MRI of the 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 2 years, >50% of cases are seizure-free on or off medication.

The observational data in this study suggest that patients may have a better response to the GABAergic antiepileptic drugs, carbamazepine and oxcarbazepine. Home rescue benzodiazepines should be strongly considered given the high frequency of status epilepticus. Development should be closely monitored, as most 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 been reported previously in KdVS, emphasizing the importance of case 31 with an angiocentric glioma. This tumor type was first described in 2005,[21,22] 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.[23] 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, and Li Fraumeni syndrome are the primary genetic syndromes in which there is a clear increased glioma risk.[24] The co-occurrence of angiocentric glioma and KdVS in case 31 is unlikely to be a 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 the overall KdVS phenotype.[10]

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 nonneurologic abnormalities may be subtle in some cases and a microarray not considered prior to seizure onset.[25] 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.[26] 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 recognized by neurologists and nor its epileptology known. Herein we show common electro-clinico-radiologic 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 antiepileptic 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 for neurologists to provide appropriate management and counseling for patients and their families.

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Disclosure of Conflict of Interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Angiocentric glioma histopathology.

Table S1. Genetic information.

Table S2. Responsiveness to specific medications.

Table S3. (A) Frequency of report of MRI abnormalities. (B) MRI-reported findings of individual patients.