■ Clinical commentary

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Epileptic Disorders

Koolen-de Vries syndrome associated with continuous spike-wave in sleep

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ABSTRACT

Koolen-de Vries syndrome (KdVS) is a genetic condition caused by 17q21.31 microdeletions or pathogenic variants in *KANSL1*. Affected patients most commonly exhibit some or all of the following: neonatal hypotonia, developmental impairment, facial dysmorphic features, and congenital malformations. Epilepsy occurs in approximately half, often with phenotypes on the epilepsy-aphasia spectrum. We describe six children with KdVS found to have continuous spike-wave in sleep (CSWS) on EEG, four of whom were diagnosed with epileptic encephalopathy with CSWS and two with Landau-Kleffner syndrome. When compared with other children with CSWS on EEG, patients with KdVS may present at slightly later ages and with a longer interval between seizure diagnosis and identification of CSWS. There is no clear best treatment for children with CSWS, but two patients in our cohort were trialed on a variation of the ketogenic diet, and both reported clinical improvement. In one of the patients, the response was dramatic, and CSWS recurred when weaning of the ketogenic diet was attempted. Based on our findings, an EEG capturing a prolonged period of sleep should be arranged in any child with KdVS presenting with developmental regression or plateau, particularly if they have a preceding history of seizures.

Key words: Koolen-de Vries syndrome, developmental regression, continuous spike-wave in sleep (CSWS), sleep EEG, ketogenic diet

Koolen-de Vries syndrome (KdVS) is a genetic disorder typically characterized by neonatal hypotonia, developmental delay, moderate intellectual disability, characteristic facial dysmorphic features, and congenital malformations [1, 2]. The syndrome is caused by a common 17q21.31 microdeletion in approximately 95% of individuals, with the remaining 5% having heterozygous pathogenic variants in *KANSL1* (OMIM 612452); the gene encoding KAT8 regulatory NSL complex, subunit 1 [3-5].

Approximately half of KdVS patients have epilepsy [1, 5-7], with the typical phenotype being childhood-onset focal epilepsy [8]. A previous epilepsy phenotyping study found that seizures often had prominent autonomic features, and that status epilepticus was common [8]. The same study found that 58% of patients with seizures had experienced developmental regression [8]. The findings of the initial KdVS epilepsy phenotyping study suggested that many KdVS patients with seizures have phenotypes falling on the epilepsy-aphasia spectrum of disorders [8, 9]. Patients at the severe end of the epilepsy-aphasia spectrum may have a specific EEG pattern called continuous spike-wave in sleep (CSWS). This pattern is seen in two epileptic encephalopathy syndromes: Landau-Kleffner syndrome (LKS) in which patients have isolated language regression, and

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epileptic encephalopathy with CSWS in which the regression is more global. In 2022, the International League Against Epilepsy (ILAE) Classification Committee grouped these two syndromes together under the umbrella term "developmental and/or epileptic encephalopathy with spike-wave activation in sleep" (DEE-SWAS) [10].

Here, we present the clinical findings in six children with KdVS, all of whom had developmental regression and CSWS on EEG, emphasizing the importance of considering this diagnosis in children with this genetic condition.

Methods

We identified patients with KdVS and CSWS through a review of our clinical databases, as well as an invitation made on our behalf through the Koolen-de Vries Syndrome Foundation social media network. Thorough epilepsy phenotyping was conducted in all cases, via caregiver interview and review of patient charts. CSWS diagnosis was based on overnight EEG recording. There are varying definitions for CSWS; while many believe spike-wave discharges should occupy 85% of the sleep record, we incorporated a more inclusive spike-wave index of 50% [11, 12]. We also included patients with so-called "focal electrical status epilepticus in sleep," even though these patterns differ from classic diffuse, bilateral CSWS [13]. However, we also only included patients with a clear clinical history of developmental regression.

Whenever possible, the actual EEG recording was reviewed; however, in some situations only a report was available. When calculating spike-wave index for a given epoch, we calculated the percentage of one-second intervals in which there was at least one spike. We considered the EEG to be significantly improved when the sleep recording no longer met the above criteria for CSWS. Epilepsy syndrome diagnosis was made by the treating epileptologist, guided by the ILAE-approved website, epilepsydiagnosis.org. Changes in cognition and language were largely based on parent or clinician report, though neuropsychology reports were reviewed when available.

Results

Six patients were identified, four with the common 17q21.31 deletion and two with frameshift pathogenic variants in *KANSL1* (*table 1*). In Patient 3, the CSWS pattern was quite focal (*figure 1*), but the patient was included as regression had been documented. Patients 1-3 had been published previously (Patients 6, 10 and 28, in Myers *et al*. [8]), though only one had CSWS identified at that time. The mean age at identification of CSWS was 7.3 years (range: 6-11 years). Of the six children, five had regression in learning or cognitive function, while five had at least clear language regression. Four had clinical presentation most consistent with classic DEE-SWAS, and the remaining two the LKS subtype of DEE-SWAS. In all but one patient, seizure diagnosis significantly preceded CSWS diagnosis, with intervals ranging from 2 to 8.5 years.

All patients required treatment with multiple antiseizure medications. Of these, those that appeared to show the most consistent benefit were oxcarbazepine, carbamazepine, clobazam and valproic acid. Two patients (1 and 5) received a variation of the ketogenic diet (KD); both appeared to derive benefit, including Patient 5 who had resolution of CSWS with language and cognitive improvement, but then experienced a second regression with CSWS recurrence when KD weaning was attempted.

Discussion

This case series of six patients with KdVS and CSWS emphasizes the potential for children with this genetic condition to develop epilepsy phenotypes at the severe end of the epilepsy-aphasia spectrum. There are significant implications for clinical management, so it is crucial that clinicians consider an overnight EEG recording when evaluating children with KdVS.

When compared against cases of CSWS in general, children with KdVS and CSWS may present somewhat differently. Sonnek *et al*. recently described a retrospective cohort of 95 children with CSWS and found that the median age of CSWS diagnosis was 5.4 years with an interquartile range of 3.4-7.5 years, while in our cohort, the mean age of CSWS diagnosis was 7.3 years [14]. Furthermore, the median interval between seizure diagnosis and CSWS diagnosis was 1.3 years (standard deviation: 3.2 years), whereas in our cohort, the mean seizure-to-CSWS diagnosis interval was 4.5 years. As well, one of our patients had quite focal left posterior CSWS but, for reasons that remain unclear, had primarily cognitive regression.

From a treatment perspective, our cohort included two patients who received KD therapy; both had a positive response, including one in whom the response was very dramatic. In contrast, there were no patients treated with KD in Sonnek *et al*.'s cohort. Other authors have studied KD as treatment for CSWS with inconsistent results; however, efficacy may be better when combined with corticosteroids [15-17]. Although there have historically been concerns about the safety of combining corticosteroids and KD, there

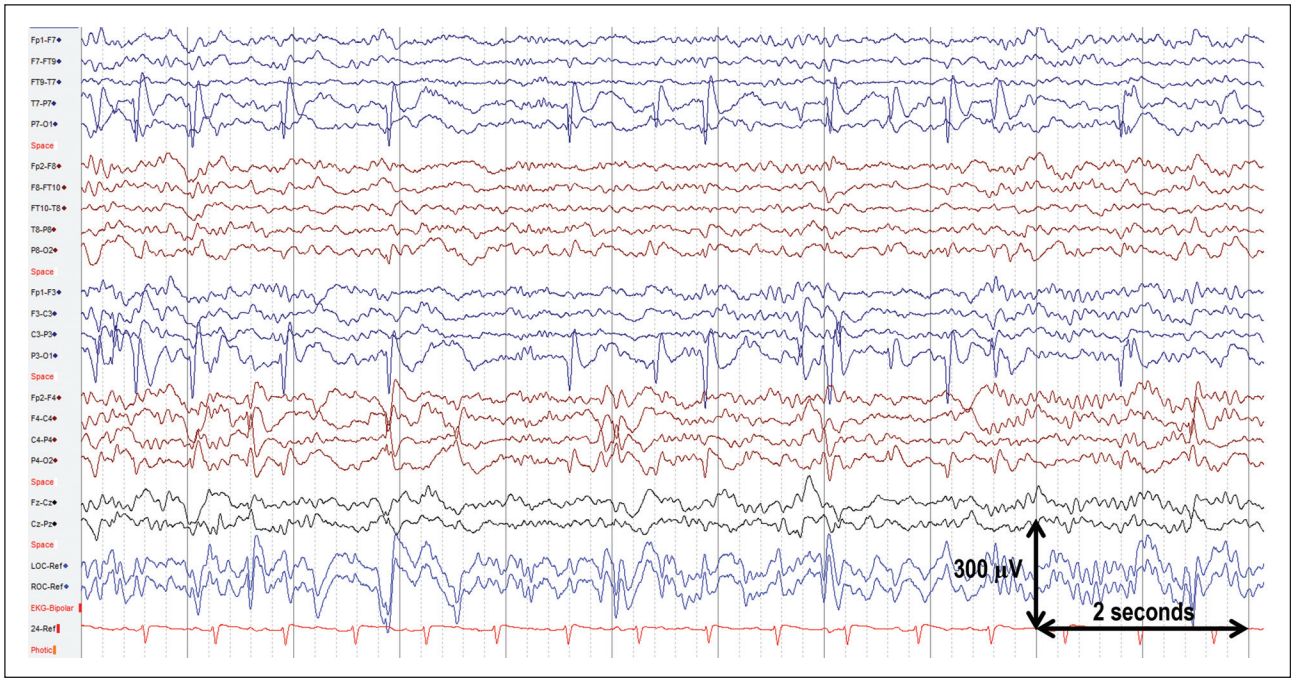
▼ **Table 1.** Clinical features of KdVS patients with CSWS.

Pt No./ Sex/ Age (y)	Del/Mut	Seizure onset	Seizure type	Seizure triggers	Epilepsy course	Developmental milestones	Age CSWS diagnosis	Regression course with CSWS	Effective treatments*	Ineffective treatments
1/F/ 10	Del	4 y	FIAS	None	Drug-resistant seizures	Sat at 9 m. Walked at 34 m. First word at 17 m. Toilet trained at 6.5 y.	7 y	Severe regression at 7 y primarily in speech and language.	VPA (only temporary benefit). Modified Atkins diet (limited clinical improvement)	Prednisone, DZP, AZM, ESM (allergic reaction), FBM
2/F/ 13	Del	0.8 y	FS (HC), FIAS, absence with eyelid myoclonia	Sleep, sickness, tiredness	Seizure-free for over 1 y.	Sat at 9 m. Walked at 2 y. First word at 22 m. Toilet trained at 7 y.	6 y	Regression not noted until 7-8 y, with deterioration in learning, speech and behaviour and cognitive function. Diagnosed with absence with eyelid myoclonia at that time. Development slowly began to improve after seizures treated.	CBZ, VPA and LVT	None
3/F/ 13	c.531_540del, p.G179fs	5 y	FIAS (autonomic and atonic features), FBTC	Febrile illnesses	Seizures began as recurrent focal status epilepticus (often provoked by illness) from age 5 to 7 y. Continued to have daily non-debilitating FIAS and weekly FBTC with variable periods of clinical seizure freedom.	Walked at 3 y. First word at 5 y. At 12 y: speaks in sentences, reads 5th grade-level sight words, mainstream classes; special education in math and writing.	11 y	Mild regression per teacher report; no clear language regression. Neuropsychiatric assessment at age 13 y, after CSWS resolution, revealed continued but slow cognitive and developmental gains over time, with a diagnosis of mild-moderate ID.	CBD, ZNS, OXC	LVT
4/M/ 11	Del	3 y	FIAS	Sleep	Seizure-free for 4 y	Sat at 6 m. Walked at 22 months. First words at 2 y.	5 y	Regression or plateauing in verbal and non-verbal skills between 4.5 y and 6.25 y. Gradual improvement of intellectual ability with age. CSWS on EEG resolved by aged 6.	Sulthiame, CLB, CBZ	LVT, VPA

▼ **Table 1.** Clinical features of KdVS patients with CSWS (*continued*).

Pt No./ Sex/ Age (y)	Del/Mut	Seizure onset	Seizure type	Seizure triggers	Epilepsy course	Developmental milestones	Age CSWS diagnosis	Regression course with CSWS	Effective treatments*	Ineffective treatments
5/F/ 15	Del	1.5 y	Bilateral TC, absences, FIAS.	None	Seizure-free for 11 months on modified KD and OXC	Sat at 11 m. Walked at 2.5 y. First word at 2 y. Has moderate ID.	10 y	Mostly speech regression; was speaking in full sentences but regressed to 2-word sentences with frequent stuttering. Also had cognitive difficulties, *e.g.*, could not remember which appliance was the refrigerator. Regressed again when KD wean was attempted.	KD, CLB, OXC	LVT
6/F/ 5.8	c.985-_del, p. Leu329Glufs*22	5 y	Bilateral TC, absences	None	EEG became free of epileptiform discharges on combination of ESM, VPA, CLB, LTG	Sat at 6 months; walked at 9 months; babbles at 6 months; first words at 12 months with dysarthria due to the cleft palate; subsequent normal developmental milestones; at 5 y, no motor deficits but communication difficulties.	5 y	Isolated language regression.	ESM, VPA, CLB, LTG	None

*Treatments were considered effective if there was clear improvement in any or all of the following: seizure frequency, development, or frequency of epileptiform discharges on EEG.
AZM: acetazolamide; CBD: cannabidiol; CBZ: carbamazepine; CLB: clobazam; CSWS: continuous spike-wave in sleep; Del: deletion; DZP: diazepam; EEG: electroencephalogram; ESM: ethosuximide; FBM: felbamate; FBTC: focal to bilateral tonic-clonic seizure; FIAS: focal impaired awareness seizure; FS: febrile seizures; ID: intellectual disability; KD: ketogenic diet; LVT: levetiracetam; Mut: point mutation; OXC: oxcarbazepine; VPA: valproic acid; ZNS: zonisamide.



■ **Figure 1.** EEG showing focal CSWS: EEG during sleep for Patient 3 at age 11 years. Abundant spike-wave discharges are seen, maximal over the left parieto-occipital region, but with a broad field that extends to the right occipital area.

is now a preponderance of evidence indicating that the combination is safe [16]. Interestingly, carbamazepine/oxcarbazepine were effective in all four patients in whom they were tried, even though these agents have been reported to exacerbate CSWS in some individuals [18]. In general, however, the treatment trends observed must be interpreted with caution given the small number of patients in our cohort.

In summary, patients with KdVS may present with DEE-SWAS, though the overall incidence in the KdVS population as a whole remains unknown. Children with KdVS tend to have CSWS diagnosed at an older age, and after a greater time interval from seizure onset, thus an EEG capturing a prolonged period of sleep should be considered essential in any child with KdVS who presents with developmental regression or plateau at any time. From a treatment perspective, no single therapy is clearly efficacious; however, KD should be considered early on for drug-resistant patients. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) When compared with other children with CSWS, do children with KdVS tend to be diagnosed with CSWS when they are older, younger, or the same age?

(2) When comparing children with KdVS to other children with CSWS, how does the interval between seizure onset and CSWS tend to differ?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.