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Diaper changing-induced reflex seizures in CDKL5-related epilepsy

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ABSTRACT – Mutations in the *CDKL5* (cyclin-dependent kinase-like-5) gene are known to determine early-onset drug resistant epilepsies and severe cognitive impairment with absent language, hand stereotypies, and deceleration of head growth. Reflex seizures are epileptic events triggered by specific stimuli and diaper changing is a very rare triggering event, previously described in individual cases of both focal and unclassified epilepsy, as well as in Dravet syndrome. Our aim was to describe diaper changing-induced reflex seizures as one of the presenting features in a case of CDKL5-related epilepsy, providing video-EEG documentation and focusing discussion on hyperexcitability determined by the disease. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: reflex seizure, diaper changing-induced reflex seizure, rub epilepsy, CDKL5-related encephalopathy

CDKL5 is a gene located on chromosome Xp22, which encodes cyclin-dependent kinase-like-5, a protein implicated in neuronal development and morphogenesis, whose the precise functions remain unknown. Mutations in *CDKL5* have been largely described in patients with early-onset drug-resistant epilepsies and cognitive impairment with absent language, hand stereotypies, and deceleration of head growth (previously characterized as "Rett-like" features). Focal seizures are often the first presentation of the disease, with onset usually before five months of age. The epileptic phenotypes then include infantile spasms and myoclonic encephalopathy (Guerrini and Parrini, 2012; Fehr *et al*., 2016).

Reflex seizures are epileptic events triggered by specific stimulation (motor, sensory or cognitive), frequently occurring in association with spontaneous seizures (Gastaut and Tassinari, 1966; Striano *et al*., 2012). Among the different types of seizures, diaper changing-induced reflex seizures, although very rare, have already been described and are considered as a possible variant of sensory reflex seizures. In particular, some authors suggested that diaper changing-induced reflex seizures represent a subtype of the so-called

VIDEO ONLINE

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"rub epilepsy" otherwise known as "rub-evoked reflex epilepsy" (RERE) (Koul *et al*., 2016).
Only one patient with CDKL5-related epilepsy has previously been reported to have reflex seizures (Saitsu *et al*., 2012). Our aim was to describe diaper changing-induced reflex seizures as initial clinical presentation in a patient affected by CDKL5-related encephalopathy.

Case study

Our patient was the second child of non-consanguineous parents, without a familial history of epilepsy. Pregnancy was characterized by "placenta previa", delivery occurred at term, and the perinatal period was unremarkable; at birth, auxological parameters were normal and she had no feeding difficulties.
From the second month of life, the baby started presenting with sudden isolated synchronous movements of the lower limbs during feeding and diaper changing. During sleep, she presented with paroxysmal events characterized by eyes opening and lateral deviation of the eyes, followed by diffuse stiffness and jerks of all four limbs.
A first interictal EEG and brain MRI were normal. Treatment with carbamazepine was started with initial efficacy. At the age of three months, she started presenting with focal seizures, followed by a series of spasms (flexion of the lower limbs and adduction of the upper limbs) during diaper changing, several times a day. She was hospitalised; psychomotor development was normal (QG Griffith's scale: 126) and only excessive startle reactions were evident on neurological evaluation. Metabolic investigations were unremarkable.
Interictal EEG showed sporadic epileptic discharges in bilateral centro-parietal regions, both during wakefulness and sleep (*figure 1A, B*). Furthermore, polygraphic recordings revealed the presence of myoclonic jerks, asynchronous on right and left limbs (*figure 1A, B*); back-averaging analysis demonstrated the cortical origin of the myoclonus (*figure 1C, D*). During EEG recordings, we documented focal seizures induced by diaper changing; the events clinically started with staring, related to EEG rhythmic theta activity in centro-parietal regions, followed by diffuse stiffness and rhythmic contractions of the four limbs, evolving into a series of spasms with predominant bending of the lower limbs (*figure 2, video sequence*). Spontaneous seizures with similar clinical and EEG features were recorded during sleep. During video-EEG monitoring, several attempts to evoke seizures by tactile stimulation or by any other single manoeuvre involved diaper changing were unsuccessful. Additionally, we noticed a refractory period after seizures, during which it was impossible to evoke them.
Benzodiazepines provided a good response only against isolated myoclonic jerks. Therapeutic attempts with topiramate and valproate were ineffective; phenobarbital led to only a reduction in seizure frequency and duration. Subsequently, reflex seizures disappeared gradually and seizures continued to recur only spontaneously, especially during drowsiness and sleep. Since nine months, psychomotor delay and midline stereotypies became evident. The interictal EEG worsened progressively and since the age of 14 months, showed multifocal epileptic discharges, becoming more frequent with eyes closed. At the same time, the patient started to present clusters of spasms, apparently not associated with focal seizures. Treatment with a combination of clonazepam, phenobarbital, and valproate was followed by a two-month seizure-free period, representing either a response to AEDs or spontaneous remission ("honeymoon period").
Next-generation sequencing analysis (using an epilepsy gene panel with 109 genes) revealed a *de novo* frameshift mutation in the *CDKL5* gene. The variant (c.580_581del) is considered pathogenic and is not reported in either the literature or the Human Genetic Mutation Database (HGMD).

Discussion

The clinical course of our patient, characterized by early-onset focal seizures, followed by progression to epileptic encephalopathy with psychomotor regression and drug-resistant epilepsy, as well as the occurrence of a seizure-free "honey-moon" period, is typical of CDKL5-related encephalopathy (Bahi-Buisson *et al*., 2008).
However, to our knowledge, there is only one published report of CDKL5-related encephalopathy with reflex seizures, which are described as massive myoclonic or generalized tonic seizures, induced by light or phone (Saitsu *et al*., 2012). The particular type of reflex seizure in our patient, induced by diaper changing, reflects a very rare condition and, to date, has never been described in CDKL5-related encephalopathy. In fact, this type of reflex seizure has been described only in a few cases; one patient with focal epilepsy of unknown aetiology (Feyissa *et al*., 2016), one with unclassified epilepsy associated with cerebellar hypoplasia (Koul *et al*., 2016), and a patient affected by Dravet syndrome (Subki *et al*., 2016).
Reflex seizures characterize either conditions in which the epileptogenic area is limited and strictly related to a triggering mechanism (*e.g*. somato-sensorial stimuli related to parietal cortical malformations) (Gastaut and Tassinari, 1966; Striano *et al*., 2012), or conditions of diffuse cortical hyperexcitability (*e.g*. Dravet syndrome, Rett syndrome). Regarding the latter, in Dravet syndrome, various triggers have been described, especially those inducing elevated body temperature (Bureau and Dalla Bernardina, 2011); in

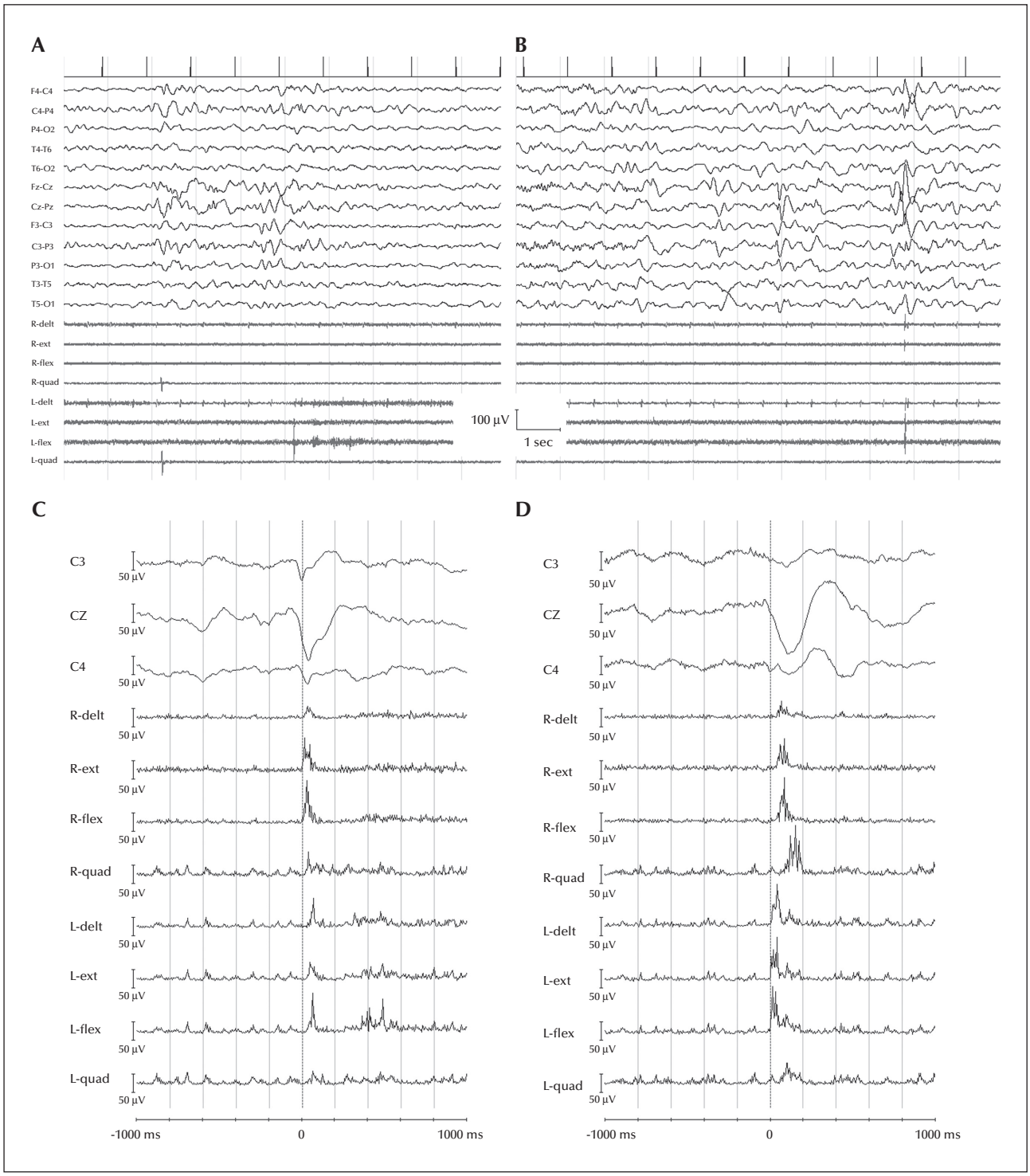

Figure 1. (A, B) Interictal EEG during sleep shows sporadic isolated spikes in the vertex region and both right and left centro-parietal regions, often related to single myoclonic jerks of the lower limbs (A) or upper limbs (B), asynchronous on the two sides. (C, D) Back-averaging of 30 different myoclonic events (trigger channel R-flex and L-flex, respectively): note that in both cases, there is evidence of agonist muscle co-contraction, followed by a contralateral myoclonic event (probably due to a propagation of the discharge); the myoclonic event is preceded by a positive transient discharge maximal on the central vertex and central region in the hemisphere contralateral to the earliest myoclonic potential. EMG abbreviations: R-delt: right deltoideus; R-ext: right extensor carpi; R-flex: right flexor carpi; R-quad: right quadriceps femoris; L-delt: left deltoideus; L-ext: left extensor carpi; L-flex: left flexor carpi; L-quad: left quadriceps femoris.

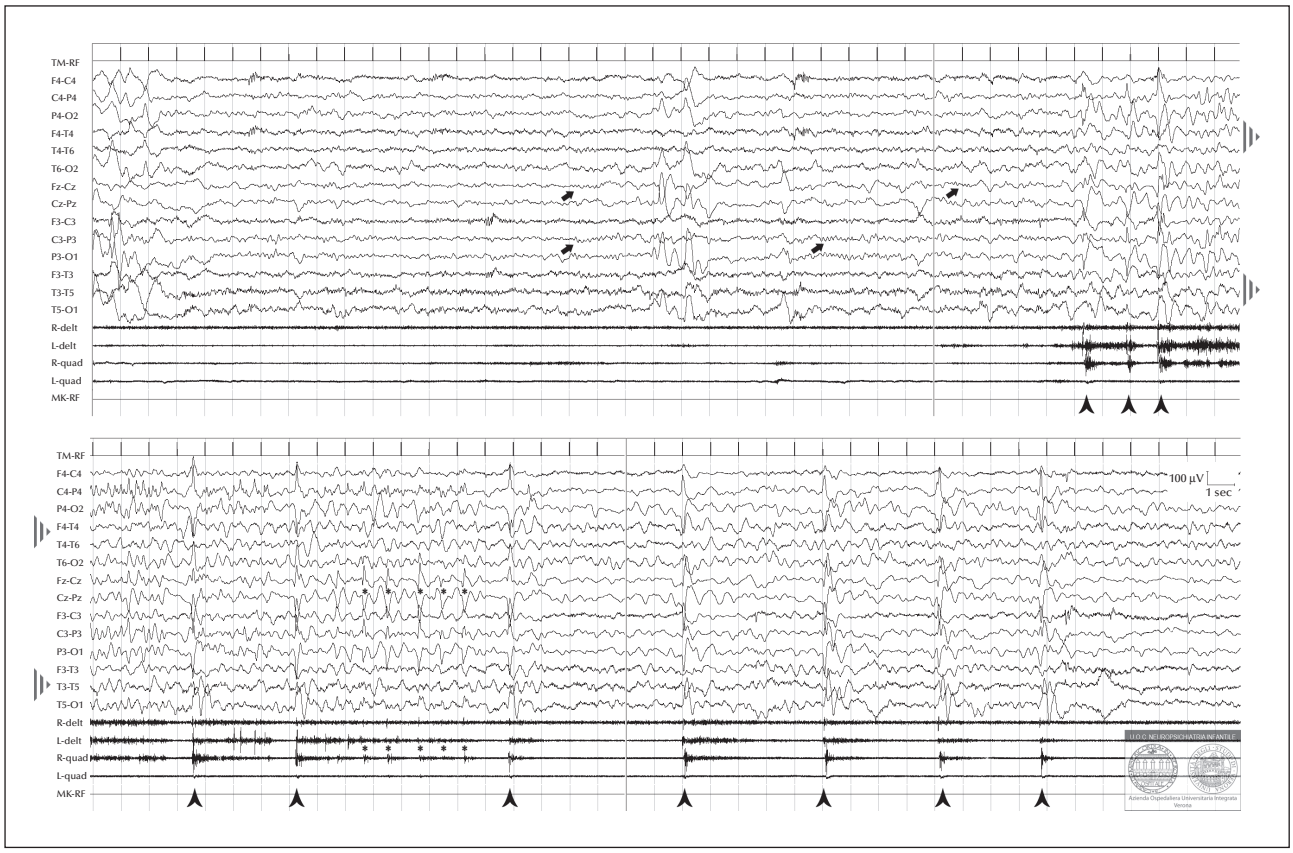

Figure 2. Ictal polygraphic recording during diaper changing (upper panel and lower panel are consecutive): the seizure starts with paroxysmal low-voltage rhythmic theta activity in the left centro-parietal and vertex regions (arrows), followed by generalized delta activity and a series of spasms, characterized by high-voltage slow complexes related to EMG periodic contractions of the four limbs (arrowheads). Note that the muscular contractions are characterized by an abrupt onset, which corresponds clinically to a "myoclonic" component (*see video*). The first spasms coincide with a tonic contraction lasting for 7-8 seconds (from the first arrowhead in the upper panel to the first three seconds of the lower panel). In the lower panel, between the second and third spasm, there is a sequence of focal spikes involving the vertex and left centro-parietal regions, each related to a myoclonic jerk of the right limbs (black asterisks). R-delt: right deltoideus; R-quad: right quadriceps femoris; L-delt: left deltoideus; L-quad: left quadriceps femoris.

Rett syndrome, there are only three reports of reflex seizures (eating-triggered and proprioceptive seizures) (Roche Martínez *et al*., 2011). In both these conditions, cortical myoclonus is frequently observed (Guerrini *et al*., 1998; Canafoglia *et al*., 2017). In our patient, we similarly documented both reflex seizures and cortical myoclonus at the same time.

Considering the triggering aspect, based on the multitude of triggering mechanisms of epileptic seizures (Gastaut and Tassinari, 1966; Striano *et al*., 2012), it is difficult to precisely classify the diaper changing-induced reflex seizures. In fact, it is difficult to discriminate between a precise stimulus or combination of events that act as the precipitating factor, considering the many variables of a complex process such as diaper changing. Cirignotta *et al*. first described seizures occurring after diaper changing, but in their case, onset of seizures occurred after the complete dressing process and the authors suggested a triggering mechanism involving the emotional gratification of being completely dressed (Cirignotta *et al*., 1982). Even if the triggering mechanism is more complex (involving also emotional factors and probably related to diffuse network hyperexcitability), the hypothesis of a crucial role of somatosensory stimulation of the perianal region has been suggested by other authors (Feyissa *et al*., 2016). This mechanism, characterized by a discharge involving primarily the post-central gyrus with spreading to the supplementary motor area, is supported in our case by the centro-parietal seizure onset visible on the EEG.

The prolonged and repetitive stimulation led some authors to hypothesize that diaper changing-induced reflex seizures represent a subtype of "rub epilepsy" or RERE (Koul *et al*., 2016). In this regard, in our patient, we observed a refractory period that has already been described in RERE, as a possible consequence of hyperpolarisation after epileptic depolarization (Kanemoto *et al*., 2001).

RERE is a rare form of somatosensory reflex epilepsy in which prolonged or repetitive cutaneous stimulation induces a seizure. It was initially described in

older patients with normal neurological examination and focal epilepsy, with seizures characterized by Jacksonian sensation, followed by unilateral tonic seizures (Kanemoto *et al*., 2001). It has also been described in other conditions, such as early-onset focal clonic seizures secondary to parietal dysplasia in Turner syndrome (Magara *et al*., 2015).

However, RERE has been described mostly in patients with unilateral stimulation reflex seizures characterized by stereotyped symptoms (Kanemoto *et al*., 2001) that are different from diaper changing-induced reflex seizures. Thus, the latter could be a more complex mechanism, involving also emotional factors and probably related to conditions of diffuse cortical hyperexcitability.

In conclusion, we would like to emphasize that reflex seizures may represent one of the presenting features of cortical hyperexcitability in CDKL5-related encephalopathy, and we suggest that diaper changing-induced reflex seizures can be considered a type of reflex seizure, possibly distinct from RERE, of which the mechanism requires further investigation. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

Legend for video sequence

Video recording of a seizure during diaper changing (same event as in *figure 2*): while the mother is cleaning the perianal region, the baby changes her facial expression and then starts to present with a series of spasms involving all four limbs. The first spasms coincide with a tonic-vibratory contraction and the following spasms then manifest as a predominant bending of the lower limbs. From second 15 to 19, a series of myoclonic jerks involving the right limbs is evident, mainly of the upper limb, during its slow adduction.

Key words for video research on www.epilepticdisorders.com

Phenomenology: spasms, focal seizure, myoclonus
Localization: centro-parietal and vertex regions
Syndrome: epileptic encephalopathy
Aetiology: genetic disorder

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TEST YOURSELF

(1) Are there many descriptions of reflex seizures in CDKL5-related epilepsy?

(2) What is "rub epilepsy"?

(3) Is there a specific type of epilepsy in which diaper changing-induced reflex seizures have been reported?

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