Clinical commentary

Epileptic Disord 2020; 22 (2): 214-8

Praxis-induced reflex seizures in two Japanese cases with ring chromosome 20 syndrome

Hirokazu Yamagishi, Masahide Goto, Hitoshi Osaka, Mari Kuwajima, Kazuhiro Muramatsu, Takanori Yamagata

Department of Paediatrics, Jichi Medical University, Shimotsuke, Japan

Received April 26, 2019; Accepted December 29, 2019

ABSTRACT – Ring chromosome 20 syndrome is an epileptic and neurodevelopmental encephalopathy that occurs in children, characterised by a triad of refractory frontal lobe seizures, recurrent non-convulsive status epilepticus and frontal lobe-dominant paroxysmal discharges. However, details of other clinical features associated with ring chromosome 20 syndrome remain unknown. Here, we report two patients with ring chromosome 20 syndrome who had praxis-induced reflex seizures. *Case 1* was an 11-year-old girl who presented with seizures triggered by specific activities such as mental and written calculations, writing, decision-making, recall, sudden changes in routine or ambient temperature and bathing. During calculations, left frontal lobe-dominant, 3-Hz slow-wave bursts were observed on EEG. Lacosamide effectively suppressed her tonic seizures. *Case 2* was a six-year-old boy who presented with seizures triggered by specific activities such as calculations, recall and bathing. During calculations, frontal lobe-dominant, 3-Hz spike and slow-wave bursts were observed on EEG. Although his epilepsy was refractory, gabapentin reduced the frequency of focal seizures. In both cases, the hyperexcitability in the frontal lobe may have spread to the motor cortex and precipitated praxis-induced seizures. Therefore, in addition to the known characteristic triad, praxis-induced reflex seizures may also be a feature of ring chromosome 20 syndrome.

Key words: ring chromosome 20, non-convulsive status epilepticus, praxis-induced seizure, reflex seizure

Ring chromosome 20 syndrome (R20) is refractory epilepsy that occurs in childhood. Classically, R20 is characterised by a triad of signs: mild to moderate intellectual disability, behavioural changes and epilepsy (for a review see Genton *et al*., 2019). Recently, the primary features of R20 have been described as the following three electroclinical characteristics: refractory frontal lobe seizures, recurrent non-convulsive status epilepticus (NCSE) and typical EEG findings including long-lasting, high-voltage slow waves or frequent trains of theta waves in the frontotemporal areas (Gago-Veiga *et al*., 2018). However, detailed cytogenetic and epileptic mechanisms and clinical features of R20 are still unknown. Conversely, in patients with reflex epilepsy,

Correspondence:
Masahide Goto
Department of Paediatrics,
Jichi Medical University,
3311-1, Shimotsuke,
Tochigi 329-0498, Japan
<mgoto@jichi.ac.jp>

doi:10.1684/epd.2020.1146

seizures may be induced by specific conditions such as reading and exposure to flickering light or unexpected touch (Ferlazzo *et al*., 2005). Seizures triggered by current thoughts such as calculations and decision-making are referred to as praxis-induced seizures (Inoue *et al*., 1994), which are strongly linked to idiopathic generalised epilepsy, particularly juvenile myoclonic epilepsy (Yacubian and Wolf, 2014).

Here, we report the cases of two patients with R20 who were experiencing seizures due to factors such as concentrated thoughts (*e.g.* performing calculations or decision-making) and bathing or showering with hot water. These two cases suggest that praxis-induced seizures and hot water epilepsy may also be features of R20. Furthermore, although seizures in patients with R20 are documented to be resistant to numerous drugs, these two patients responded to lacosamide and gabapentin. Informed consent was obtained from the families of both patients before performing cytogenetic analyses.

Case studies

Case 1

An 11-year-old girl, with no significant medical or family history, was born after an uneventful pregnancy and labour. She presented with episodes of staring, decreased responsiveness, ictal fear and sleep-related tonic-clonic seizures at the age of nine years. In particular, tonic seizures occurred approximately 10-15 times per day. Seizures occurred during the day and night, but she always woke up with a tonic seizure in the morning. Her developmental milestones were normal. The triggers for seizures included performing both mental and written calculations, writing, making decisions, recall, sudden changes in routine or ambient temperature and bathing. These triggers were according to the observations of her parents. The patient tried avoiding these activities to prevent seizures and occasionally appeared to experience fear during seizures.

Interictal EEG showed spontaneous 4-Hz spike and slow waves in the left frontal regions. Intermittent photic stimulation did not evoke photoparoxysmal responses. EEG monitoring over 24 hours revealed prolonged, 1.5-2-Hz spike and slow-wave complexes with mild clouding of consciousness for around 20 minutes in the absence of motor manifestations, indicative of NCSE.

The patient's physical and neurological examination was normal. Her intelligence quotient was determined to be 69 based on the Wechsler intelligence scale for children-IV (WISC-IV). Chromosomal analysis led to the diagnosis of R20 with 88% mosaicism. Array comparative genomic hybridisation revealed no deletions or duplications in any chromosomes, including chromosome 20.

Brain MRI revealed no abnormalities. Cerebral blood flow by N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP) single-photon emission computed tomography (SPECT) indicated increased tracer uptake in the left frontal area during NCSE. In contrast, N-isopropyl-p-[^{123}I]-iomazenil SPECT and fluorodeoxyglucose-positron emission tomography revealed no significant findings.

Carbamazepine, valproic acid, levetiracetam, lamotrigine, zonisamide and gabapentin were ineffective in controlling the seizures. However, lacosamide treatment decreased the tonic seizures from 10-15 times per day to 1-2 times per week and reduced the spike and slow-wave complex bursts in frontal areas observed on EEG. Before and after the treatment, the patient had no behavioural abnormality and showed no deterioration. After two years, the frequency of tonic seizures remained at 1-2 times per week owing to lacosamide, and on the interictal EEG, paroxysmal discharges were completely suppressed, however, seizures were not completely controlled. Although the administrated test was not a systematic examination, EEG monitoring conducted when the patient was performing calculations revealed left frontal lobe-dominant high-amplitude slow-wave activity of approximately 3 Hz, however, no discernible seizures were induced (*figure 1A*).

Case 2

The second case was a six-year-old boy with no significant medical or family history of disease. No complications were reported during his mother's pregnancy and delivery. His developmental milestones were normal.

At three years of age, the patient experienced seizures before going to sleep and walked around and stamped his feet during seizures. Various seizures (focal impaired awareness seizures, oral automatism and focal-to-bilateral tonic-clonic seizures) occurred 10 or more times a day. The seizures occurred during certain activities, such as performing calculations, attempting to recall a particular thing and bathing. These triggers were according to the observation of his parents. The patient appeared fearful during the seizures. Behavioural abnormalities such as emotional instability and aggressiveness were noted after the seizures subsided.

Interictal EEG showed sporadic 4-Hz spike and slow-waves in the left frontal regions. Intermittent photic stimulation did not evoke photoparoxysmal responses. EEG monitoring over 24 hours revealed

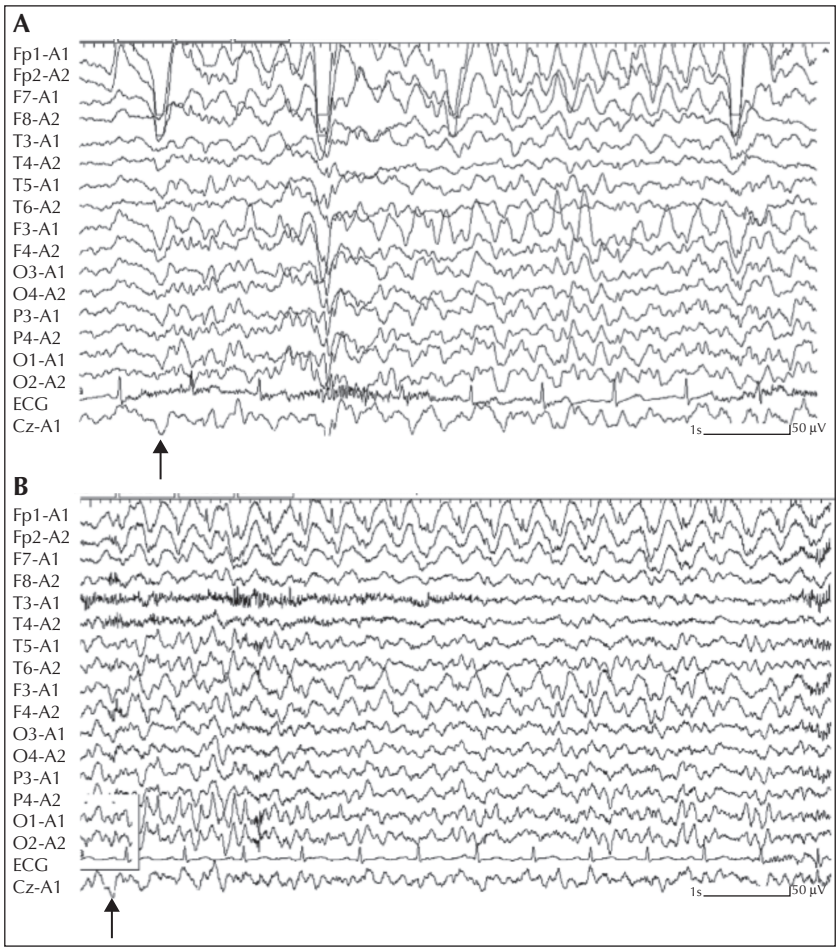

Figure 1. (A) Calculations performed by the patient during EEG recordings in Case 1. The patient was asked a mathematical question "What is 64 divided by 3?" and asked to perform the calculation. While performing, 3-Hz slow-wave bursts were detected for 10 seconds in the left frontal area (arrow). The clouding of consciousness or discernible seizures were not observed. (B) Calculations performed by the patient during EEG recordings in Case 2. The patient was asked a mathematical question "What is 12 plus 8?" and asked to perform the calculation. While performing, 3-Hz spike and slow-wave complex bursts were detected for 20 seconds in the left frontal area (arrow). Discernible seizures were not observed.

prolonged spike and slow-wave complexes, predominantly in the frontal lobe, with mildly decreased responsiveness and no motor manifestations, indicative of NCSE.

The patient had no dysmorphism and normal neurological examinations. His intelligence quotient was determined to be 66 based on the WISC-IV. The patient was diagnosed with R20 with 63% mosaicism. Array comparative genomic hybridisation revealed no deletions or duplications in any chromosomes, including chromosome 20. Brain MRI and cerebral blood flow ^{123}I-IMP SPECT revealed no abnormalities.

Carbamazepine, valproic acid, rufinamide, lacosamide, perampanel, ethosuximide and phenytoin were ineffective in controlling the seizures. However, in addition to carbamazepine, lamotrigine and levetiracetam, gabapentin decreased the frequency of focal seizures from 10 times/day to two times/week. Nevertheless, the behaviour of the patient had gradually become aggressive. When the patient did not get what he wanted, he raised a strange voice and began to break things around him. After a year, the frequency of focal seizures (focal impaired awareness seizures and focal-to-bilateral tonic-clonic seizures) remained 2-3 times per week owing to gabapentin, and on the interictal EEG, paroxysmal discharges were completely suppressed; however, the drug did not completely control the seizures. Although the administrated test was not a systematic examination, EEG monitoring conducted when the patient was performing calculations revealed left frontal lobe-dominant high-amplitude spike and the slow-wave activity of approximately 3 Hz, however, no discernible seizures were induced (*figure 1B*).

Discussion

Typically, seizures in patients with common epilepsy are triggered by fatigue or drowsiness. In contrast, in the two cases presented here, the seizures were induced during certain activities such as performing calculations, concentrated thoughts and bathing. In both cases, the frontal lobe-dominant high-voltage slow waves were observed on EEG while the patient performed calculations, suggesting epileptogenicity of praxis-induced seizures in the cortex. If the patients had not been treated with effective drugs, such as lacosamide or gabapentin, the task of calculating would have continued to cause praxis-induced seizures. Reports on known R20 cases regarding trigger factors revealed that video games, psychological stress and bathing were seizure-inducing factors (Takahashi *et al*., 1995; Inoue *et al*., 1997; Gomes *et al*., 2002; Yalçin *et al*., 2006; Watson *et al*., 2015; Vignoli *et al*., 2016). One case study reported in detail that mental calculation elicited a high-voltage spike-wave rhythm without any clinical symptoms (Takahashi *et al*., 1995). Similarly, we confirmed findings that the frontal lobe-dominant high-voltage slow waves were observed when both the patients performed the calculations.

Praxis-induced seizures have an underlying ictogenic mechanism associated with hyperexcitability of the functional anatomical central nervous system network, physiologically subserving visuomotor coordination (Yacubian and Wolf, 2014). Additionally, the hyperexcitability of the sensorimotor cortex linked to other areas by the corticocortical pathways is necessary to trigger seizures, and the hyperexcitability can be activated by the thinking process (Inoue and Zifkin, 2004). As the current cases exhibited hyperexcitability in the frontal lobe, the hyperexcitability may have spread to the motor cortex through transcortical tracts and precipitate praxis-induced seizures by external or internal stimuli. R20 can easily progress to NCSE, in which frontal lobe-dominant, high-voltage, slow or theta waves are revealed on EEG; therefore, the electrical activity in the brain appears to be in a constant state of hyperexcitability. Susceptibility to seizures induced by external or internal stimuli, such as those in praxis-induced reflex seizures, may be a feature of R20.

Although the patient in Case 1 had various triggers, such as writing, making decisions, sudden changes in routine and ambient temperature, the patient in Case 2 had no such triggers. It is important to consider the seizure or background to understand the specificity of the triggers. However, a limitation of this study was that these triggers could not be determined accurately because the examinations were not systematic (they consisted of interviews with the parents of the patients). Furthermore, regarding other complex triggers such as speaking/reading, memory, emotion, non-cognitive movement or more elementary sensory-motor activities, it is difficult to explain the whole mechanism based on hyperexcitability of the functional network in the multiple lobes. To elucidate the complex mechanisms between various precipitations and epileptogenic foci, appropriate neurophysiological examinations during each triggering task would be required.

Both patients presented herein exhibited ictal fear. A study on R20 reported ictal fear in 13 of 25 cases (52%) and terrifying hallucinations in six of 24 patients (25%) (Vignoli *et al*., 2016). Intracranial EEG analysis during seizures with ictal fear suggested the involvement of the amygdala (Biraben *et al*., 2001). In this study, both patients were found to have epileptogenic zones in the frontal lobe, as assessed using ictal EEG or ^{123}I-IMP SPECT, which may have spread to the amygdala through transcortical tracts and have caused ictal fear.

Notably, R20 is refractory to treatment with most drugs. A combination of valproic acid and lamotrigine was reportedly helpful in treating seizures in patients with R20 (Vignoli *et al*., 2009). This combination should also be considered as patients grow older because NCSE usually increases in frequency in patients with R20 when they reach adolescence. In addition, only one case of R20 was reported to benefit from lacosamide (Onder and Tezer, 2016). In the current cases, lacosamide and gabapentin were effective in each patient, respectively. The mechanism of action of lacosamide is the prevention of channel opening via slow inactivation of components of voltage-gated sodium channels (Onder and Tezer, 2016). Gabapentin reduces potassium-evoked excitatory amino acid release by inhibiting P/Q-type calcium channels (Fink *et al*., 2000), and promptly elevates brain gamma-aminobutyric acid (GABA) levels (Petroff *et al*., 2000). Lacosamide is an exclusive slow sodium channel blocker; gabapentin has the same pharmacological function as a calcium channel inhibitor of low-voltage activated type (*e.g.* lamotrigine) and has the same GABAergic inhibition as valproic acid. Although we cannot determine whether the observed result was due to the combined effect of drugs or a reciprocal action between the drugs, lacosamide and gabapentin combined with valproate acid and lamotrigine should be considered for the treatment of patients with R20.

In conclusion, R20 should be considered in patients who present with the characteristic triad as well as praxis-induced reflex seizures. The clinical history associated with potential factors triggering seizures can easily be overlooked. Although lacosamide and

gabapentin combined with valproate acid and lamotrigine may be useful for the treatment of R20, further studies are needed to validate the efficacy of this combination of drugs. □

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

Acknowledgements and disclosures.
We thank Kensuke Kawai of the Department of Neurosurgery and the staff of the electroencephalographic examination room at the Jichi Medical University Hospital.
None of the authors have any conflict of interest to declare.

References

Biraben A, Taussig D, Thomas P, *et al*. Fear as the main feature of epileptic seizures. *J Neurol Neurosurg Psychiatry* 2001; 70(2): 186-91.

Ferlazzo E, Zifkin BG, Andermann E, Andermann F. Cortical triggers in generalized reflex seizures and epilepsies. *Brain* 2005; 128(Pt 4): 700-10.

Fink K, Meder W, Dooley DJ, Göthert M. Inhibition of neuronal Ca (2+) influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices. *Br J Pharmacol* 2000; 130: 900-6.

Gago-Veiga AB, Toledano R, García-Morales I, Pérez-Jiménez MA, Bernar J, Gil-Nagel A. Specificity of electroclinical features in the diagnosis of ring chromosome 20. *Epilepsy Behav* 2018; 80: 215-20.

Genton P, Marini C, Bahi Buisson N, Kaminska A, Elia M, Gobbi G. Ring chromosome 20 syndrome. In: Bureau M, Genton P, Delgado-Escueta A, *et al*, eds. *Epileptic syndromes in infancy, childhood and adolescence*, 6th ed. Montrouge: John Libbey, 2019.

Gomes Mda M, Lucca I, Bezerra SA, Llerena Jr. J, Moreira DM. Epilepsy and ring chromosome 20: case report. *Arq Neuropsiquiatr* 2002; 60(3): 631-5.

Inoue Y, Seino M, Tanaka M, Kubota H, Yamakaku K, Yagi K. Epilepsy with praxis-induced seizures. In: Wolf P, ed. *Epileptic seizures and syndromes*. Montrouge: John Libbey, 1994.

Inoue Y, Fujiwara T, Matsuda K, *et al*. Ring chromosome 20 and nonconvulsive status epilepticus. A new epileptic syndrome. *Brain* 1997; 120(Pt 6): 939-53.

Inoue Y, Zifkin BG. Praxis induction and thinking induction: one or two mechanisms? A controversy. In: Wolf P, Inoue Y, Zifkin B, eds. *Reflex epilepsies: progress in understanding*. Montrouge: John Libbey Eurotext, 2004.

Onder H, Tezer FI. Significant improvements of EEG and clinical findings with oral lacosamide in a patient with ring chromosome 20. *Clin EEG Neurosci* 2016; 47(4): 330-2.

Petroff OA, Hyder F, Rothman DL, Mattson RH. Effects of gabapentin on brain GABA, homocarnosine, and pyrrolidinone in epilepsy patients. *Epilepsia* 2000; 41: 675-80.

Takahashi Y, Shigematsu H, Kubota H, *et al*. Nonphotosensitive video game-induced partial seizures. *Epilepsia* 1995; 36: 837-41.

Vignoli A, Bisulli F, Darra F, *et al*. Epilepsy in ring chromosome 20 syndrome. *Epilepsy Res* 2016; 128: 83-93.

Vignoli A, Canevini MP, Darra F, *et al*. Ring chromosome 20 syndrome: a link between epilepsy onset and neuropsychological impairment in three children. *Epilepsia* 2009; 50: 2420-7.

Watson A, Watson D, Taylor C. Life with r(20)-Ring chromosome 20 syndrome. *Epilepsia* 2015; 56(3): 356-8.

Yacubian EM, Wolf P. Praxis induction. Definition, relation to epilepsy syndromes, nosological and prognostic significance. A focused review. *Seizure* 2014; 23(4): 247-51.

Yalçin AD, Toydemir HE, Forta H. Hot water epilepsy: clinical and electroencephalographic features of 25 cases. *Epilepsy Behav* 2006; 9(1): 89-94.

TEST YOURSELF

(1) What are the three features of ring 20 chromosome syndrome?

(2) What is a praxis-induced seizure?

(3) What were the effective drugs for the patients with ring 20 syndrome reported in this case study?

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".