

Intractable epilepsy, growth failure, hypothyroidism, and cataract: rare clinical manifestations in a patient with ring chromosome 20 syndrome

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Abstract

Ring chromosome 20 [r(20)] syndrome is typically characterized by intractable epilepsy, variable degrees of behavior problems and cognitive deficits, and an absence of or minimal dysmorphic features. Here we report a case diagnosed with r(20) syndrome exhibiting rare clinical manifestations of intractable epilepsy, growth failure, hypothyroidism, and cataract. This 17-year-old female patient who showed growth failure and no dysmorphic features had the first seizure at the age of 8 years. The seizure pattern was described as periods of non-convulsive status epilepticus with prolonged confusional state, motionless stare, mutism, and subtle motor seizures, lasting for minutes to hours. The interictal EEG showed bilateral synchronous, rhythmic high voltage delta waves intermixed with occasional spikes over the bilateral frontal areas. The seizures were refractory to medical treatments. Hypothyroidism and cataract were subsequently diagnosed at the age of 16 years and 17 years, respectively. Chromosome study showed a female genome with r(20) mosaicism. In conclusion, r(20) syndrome might cause multisystemic involvement, and therefore, comprehensive surveys of the central nervous system, ophthalmologic system, and endocrine system, among others, are crucial.

Keywords: Cataract; hypothyroidism; intractable epilepsy; ring chromosome 20

INTRODUCTION

Ring chromosome 20 [r(20)] syndrome, first reported in 1972¹, is a rare chromosomal anomaly characterized by intractable epilepsy, behavior problems, normal cognitive function or mild to moderate cognitive deficits, and an absence of or minimal dysmorphic features in a previously developmentally normal child. This distinct syndrome has been proposed as an epileptic encephalopathy because behavior and cognition decline after the seizure.²

Epilepsy is an almost invariant feature of r(20) syndrome and is usually medically refractory. The age of onset of seizures can be anywhere between neonate and 20 years of age.³ Periods of non-convulsive status epilepticus (NCSE) and brief motor seizures are among the most common seizure types. NCSE appearing in the form of focal status epilepticus consists of a prolonged confusional state, which fluctuates and is not so

severe as to completely cause unresponsiveness or motionlessness, together with an apathetic facial expression, mutism, inattentiveness, perseveration, and slowness of response and behavior, usually lasting minutes to hours. This type of NCSE is often associated with particular electroclinical features in the form of concomitant long-lasting, bilateral synchronous, rhythmic high-voltage slow waves with occasional spikes, usually frontal, whereas spike-and-wave complexes are not a predominant feature.^{3,4} This epileptic state may accompany additional motor seizures or convulsive seizures. Other seizure types include ictal terror, ictal visual hallucination, gelastic seizures, motor automatism, or tonic activity.^{4,5}

In contrast with inevitably medically intractable epilepsy in patients with r(20) syndrome, cognitive and behavior problems as well as dysmorphic features are not typically found. Minimal dysmorphic features, including microcephalus,

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ocular exotropia, large and cauliflower-shaped ears, sparse teeth, frontal bossing, epicanthal folds, low nasal bridge, and short stature with or without growth hormone deficiency have been reported^{1,3,6-7}, however, other systemic problems have never been mentioned.

Here we report a 17-year-old girl had experienced intractable epilepsy since the age of 8 years and was subsequently diagnosed with hypothyroidism and cataract at the age of 16 years and 17 years, respectively. Ring chromosome 20 was identified by karyotype analysis. To the best of our knowledge, this is the first description of multisystemic involvement in r(20) syndrome.

CASE REPORT

This 17-year-old female patient was born after an uneventful full-term pregnancy. The family history was unremarkable. The girl developed normally in early childhood.

At the age of 8 years, she began to have seizures in which she exhibited emotional lability at the beginning of the seizure followed by clouding of consciousness with eye opening, staring, slow activity, and intermittent mild clonic seizures of bilateral upper limbs, as well as purposeless behavior, tremors of the mouth, and jerking and shaking of the trunk. The seizure durations were 5 to 90 minutes. The seizure frequency was 1 to 3 times daily. She also had another type of seizure in which she looked dull with clouded consciousness

and had an apathetic facial expression with staring eyes. She also became mute accompanied by body stiffening and mild clonic seizures of bilateral hands. The seizure durations were 2 to 30 minutes. The seizure frequency was 1 to 3 times per week. Over a period of years, the attacks gradually increased in frequency despite medical management.

At the age of 16 years and 3 months, the girl visited our outpatient department. During the visit, physical examinations revealed no dysmorphic features, apparent abdominal distension and flatulence, and poor appetite. She had a slight figure with body weight of 33.5 kilograms and height of 149.5 cm. Neurologically she was normal. The interictal electroencephalography (EEG) revealed a 6-7 Hz theta wave rhythm with frequently dominant 3-4 Hz delta waves intermixed with spikes at the bilateral frontopolar and frontal regions (Figure 1). The ictal EEG showed initial appearance of 5-6 Hz theta waves over the bilateral hemispheres followed by a burst of bilateral, almost synchronous, high amplitude 2-3 Hz rhythmic delta waves predominantly over the frontal areas during the brief staring and subtle clonic movement of bilateral hands (Figure 2 a, b). The neuroimaging studies showed negative findings.

Further laboratory surveys disclosed hypothyroidism [TSH 5.56 uIU/ml (normal 0.4-4.0), T3 57.3 ng/dL (normal 84-172) and T4

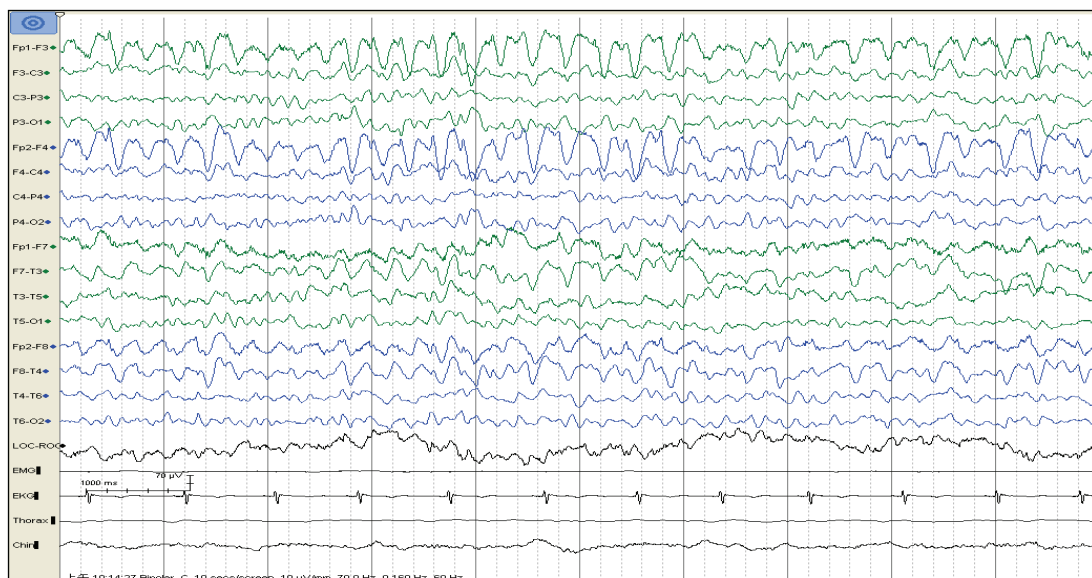


Figure 1. The interictal electroencephalography (EEG) of the patient. The bipolar EEG recording shows a 6-7 Hz theta wave rhythm with dominant 3-4 Hz delta waves intermixed with focal spikes at the bilateral frontopolar and frontal areas.

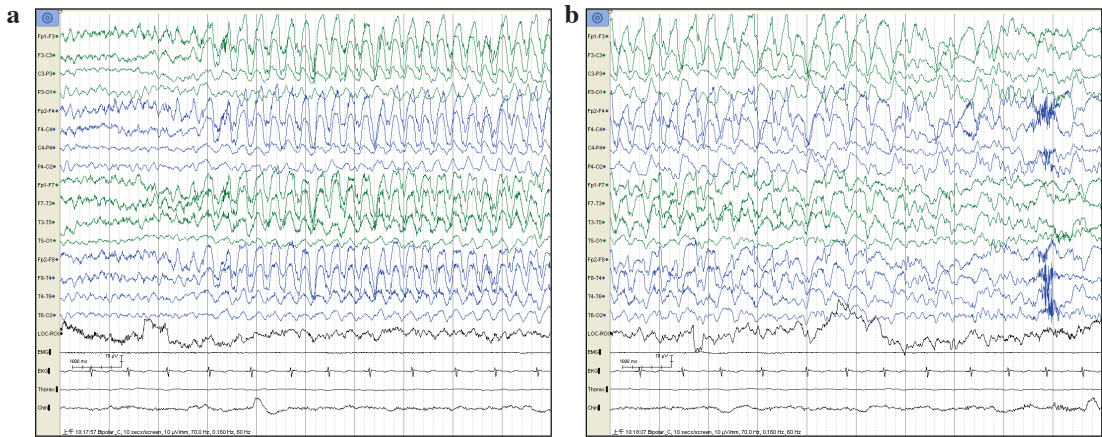


Figure 2. The ictal electroencephalography (EEG) of the patient. When the patient exhibits clinical features of brief staring and subtle clonic movement of bilateral hands, the simultaneous EEG recording shows a change from the baseline appearance of 5-6 Hz theta waves over the bilateral hemispheres followed by bilateral, almost synchronous, high amplitude 3Hz delta waves bursts (a) and 2-3Hz delta waves bursts with occasional spikes (b) predominantly over the frontopolar and frontal areas.

4.12 ug/dL (normal 4.5-12.5)], but all other studies revealed normal results. Metabolic workups were unremarkable. Ocular fundus examination revealed an initially normal result. However, at the age of 17 years, the girl complained of blurred vision and follow-up fundus examination revealed bilateral cataracts.

Routine chromosomal analysis was done on peripheral blood leukocytes indicating a female genome with mosaicism: 29 (58%) of 50 analyzed cells were 46, XX, 19 (38%) were r(20) [46, XX, r(20)(p13q13.33)], and 2 (4%) were dicentric r(20) [46, XX, dic r(20; 20)(p13q13.3; p13q13.3)] (Figure 3 a-c). The diagnosis of r(20) syndrome was made. An intelligence quotient (IQ) test [Wechsler Intelligence Scale for Children-Revised (WISC-R)] scored full IQ 64. The medications included clonazepam, oxcarbazepine, and valproic acid, as well as levothyroxine sodium.

DISCUSSION

Since r(20) syndrome was first described in 1972, more than 100 cases have been reported.⁷ Although characteristic electroclinical patterns have been well defined in this rare but distinct epilepsy syndrome^{3,8}, unlike other chromosomal disorders, the lack of specific phenotypic expression or dysmorphic features in r(20) syndrome often causes a delay in obtaining an accurate diagnosis and long misdiagnosis is responsible for many useless investigations, including metabolic surveys and extensive evaluations with multiple scalp EEGs, video EEGs, brain MRI, and cranial PET scan.

The salient features of epileptic seizures in r(20) syndrome are typically periods of NCSE, focal seizures with or without evolution to bilateral tonic-clonic seizures, and refractory to



Figure 3. Cytogenetic analysis of the patient. Of 50 analyzed cells, 29 (58%) cells are 46, XX (a), 19 (38%) are ring chromosome 20 [46, XX, r(20)(p13q13.33)] (arrow) (b), and 2 (4%) are dicentric ring chromosome 20 [46, XX, dic r(20; 20)(p13q13.3; p13q13.3)] (arrows) (c).

medical treatments. The EEG features comprise long-lasting bilateral, rhythmic high-voltage delta waves with occasional spikes over the frontal lobes interictally or during seizures. Evidence of frontal focality in scalp EEG and clinically drug-resistant epilepsy may prompt the clinical physician to consider the possibility of intractable frontal lobe epilepsy and thus recommend subsequent evaluative investigations for epilepsy surgery. However, the distinct electroclinical features of r(20) syndrome are different from those of frontal cortical malformation-related intractable epilepsy, in which a brief period of prominent focal motor seizures, with or without evolution to bilateral tonic-clonic seizures and obvious ictal focal spikes showing on the EEG, can be recorded.

Besides neurologic problems, the index case presented with growth failure, hypothyroidism, and cataract. The cause of growth failure in r(20) syndrome has been hypothesized to be related to haploinsufficiency due to specific deletions within ring chromosomes, rather than the ring itself⁹, and is also thought to be due to growth hormone deficiency.³ Many chromosomal or microchromosomal disorders, such as Down syndrome, Turner syndrome, 1q21.1 deletion syndrome, have been reported to be associated with hypothyroidism and/or cataract.¹⁰⁻¹² The signs of hypothyroidism and cataract have not been reported in patients with r(20) syndrome.

In conclusion, clinical physicians should be aware of the characteristic electroclinical pattern of r(20) syndrome so that this rare chromosomal disorder can be diagnosed earlier. r(20) syndrome is a multisystemic disorders and thus comprehensive investigations should be carried out. Understanding the whole picture of r(20) syndrome is vital as numerous useless investigations can be avoided, and the patient's family can be provided with genetic counseling.

DISCLOSURE

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Conflict of interest: None

Ethics: The study was approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB TCVGH CE17341A).

REFERENCES

1. Atkins L, Miller WL, Salam M. A ring -20 chromosome. *J Med Genet* 1972; 9:377-80.
2. Vignoli A, Canevini MP, Darra F, *et al.* Ring chromosome 20 syndrome: a link between epilepsy

- onset and neurological impairment in three children. *Epilepsia* 2009; 50:2420-7.
3. Inoue Y, Fujiwara T, Matsuda K, *et al.* Ring chromosome 20 and nonconvulsive status epilepticus: A new epileptic syndrome. *Brain* 1997; 120:939-53.
4. Ville D, Kaminska A, Bahi-Buisson N, *et al.* Early pattern of epilepsy in the ring chromosome 20 syndrome. *Epilepsia* 2006; 47:543-9.
5. Dimovs P, Boneva I, Todorova A, Minotti L, Kahane P. Gelastic seizures in ring chromosome 20 syndrome: a case report with video illustration. *Epileptic Disord* 2012; 14:181-6.
6. Conlin LK, Kramer W, Hutchinson AL, *et al.* Molecular analysis of ring chromosome 20 syndrome related two distinct groups of patients. *J Med Genet* 2011; 48:1-9.
7. Vaudano AE, Ruggieri A, Vignoli A, Canevini MP, Meletti S. Emerging neuroimaging contribution to the diagnosis and management of the ring chromosome 20 syndrome. *Epilepsy Behav* 2015; 45:155-63.
8. Radhakrishnan A, Menon RN, Hariharan S, Radhakrishnan K. The evolving electroclinical syndrome of "epilepsy with ring chromosome 20". *Seizure* 2012; 21:92-7.
9. Daber RD, Conlin LK, Leonard LD, *et al.* Ring Chromosome 20. *Eur J Med Genet* 2012; 55:381-7.
10. Counts D, Varma SK. Hypothyroidism in Children. *Pediatr Rev* 2009; 30:251-8.
11. Francis PJ, Berry V, Bhattacharya SS, Moore AT. The genetics of childhood cataract. *J Med Genet* 2000; 37:481-8.
12. Shiels A, Hejtmancik JF. Genetics of human cataract. *Clin Genet* 2013; 84:120-7.