Seeing Clowns with a Ring 20 Chromosome

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Abstract

Ring chromosome 20 syndrome is a rare genetic disorder characterized by non-convulsive status epilepticus (NCSE) attacks, leading to prolonged confusional states of varying intensity. It is often accompanied by electroencephalography (EEG) changes, such as long-lasting slow waves and occasional spikes, primarily over the frontal lobes, as well as focal seizures with visual hallucinations, cognitive impairment, and behavioral problems. Although clinical suspicion, typical EEG abnormalities, and network disorders revealed by functional neuroimaging method aid in diagnosis, karyotyping remains essential. Seizures are typically drug-resistant although some limited success has been reported with certain anti-seizure drugs. In this report, we present the case of a patient with previously frequent drug-resistant NCSE periods characterized by prolonged confusional states and frightening visual hallucinations. Treatment with lacosamide partially decreased the frequency of seizures. In addition, positron emission tomography/computed tomography (PET/CT) imaging revealed hypometabolism in the frontal and parietal regions of the brain. In patients with drug-resistant and early frightening hallucinations, consideration of the ring 20 chromosome anomaly is crucial. PET/CT imaging may demonstrate hypometabolism in the parietal and frontal lobes, potentially associated with the hallucinations and epileptogenesis of the syndrome. Lacosamide may be a viable option for reducing seizures in Ring chromosome 20 syndrome.

Keywords: Non-convulsive status epilepticus, visual hallucinations, drug-resistance, karyotyping, ring 20, lacosamide

INTRODUCTION

Ring chromosomes (RCs) are rare genetic disorders caused by intrachromosomal fusion. Among RCs, the ring 20 chromosome [r(20)] has attracted special interest because of its distinct electroclinic features, first reported in 1972.[1] The r(20) syndrome is characterized by focal seizures accompanied by visual hallucinations, prolonged confusional states, and cognitive and behavioral problems, which typically begin in childhood. Non-convulsive status epilepticus (NCSE) attacks are frequently observed. The r(20) chromosome is usually found in a mosaic state, and its specific diagnosis is made by karyotyping. While conventional cranial magnetic resonance imaging (MRI) usually does not detect any structural pathology, functional neuroimaging methods such as single photon emission computed tomography (SPECT), positron emission tomography/computed tomography (PET/CT), and fMRI have shown dysfunction in specific brain areas. In this report, we present the case of a patient with r(20) syndrome who experienced NCSE and vivid visual hallucinations, along with neuroimaging results, to raise awareness about this rare disorder.[2]

CASE PRESENTATIONS

A 19-year-old male patient was admitted with frequent seizures and attention problems. At the age of six, he started experiencing hypermotor seizures, followed by rare generalized tonic-clonic seizures. The frequency of seizures decreased with oxcarbazepine. Before the seizures, he described complex visual hallucinations, often featuring a scary clown. At the age of nine, he began experiencing periods of staring and decreased responsiveness, lasting up to 45 min and occurring 5-6 times a day.

Despite administering various anti-seizure drug treatments, including levetiracetam, zonisamide, lamotrigine, carbamazepine, valproate, topiramate, ethosuximide, and clobazam, at appropriate doses and durations, seizure control could not be achieved. At the time of admission, the patient was taking valproate 2000 mg/day and zonisamide 300 mg/day. Neurological examination revealed normal findings, except for decreased time orientation and mild cognitive retardation. The patient's medical history was unremarkable, but a distant relative on the paternal side had been diagnosed with late-onset epilepsy.

Routine laboratory tests and cranial MRI results were normal. Electroencephalography (EEG) showed diffuse slowing of background activity, sharply contoured theta activity in the anterior part of the hemispheres (Figure 1a), and generalized epileptiform abnormality interictally, along with atypical absence seizures accompanied by perioral myoclonia (Figure 1b). In addition, generalized 3-7 Hz fluctuating slow wave periods were prominent in the anterior regions, lasting 45-60 min, which were evaluated as NCSE (Figure 1c). A brain PET/CT scan revealed mild hypometabolism in the left prefrontal and bilateral parietal inferior regions (Figure 2).

Karyotype analysis from peripheral blood lymphocytes showed mos45, XY, 20/46,XY/46,XY,r(20)(p13q13.32)[4/35/51].ish r(20)(pterqter)(D20S210+/RH1656+). FISH analysis using subtelomere-specific probes for the p and q arms of chromosome 20 (Cytocell, Cambridge, UK) demonstrated the presence of both subtelomeres in r(20). A microarray study found no genomic imbalance. In 57% (51 of 90 metaphases) of cells, it was confirmed that one of the normal chromosomes of 20 was replaced by a r(20) with no genomic imbalance, establishing the diagnosis of mosaic r(20) chromosome (Figure 2). The absence of chromosome 20 in 4% of cells (4 of 90 metaphases) in the patient was considered a result of the unstable status of RCs and their tendency to be lost in dividing cells.[1] Parental karyotype analyses were performed to rule out mosaic-to-mosaic transmission, and normal results were obtained for the parents.

After initiating lacosamide treatment, the patient experienced a notable improvement in his condition. Focal seizures with visual hallucinations ceased, and the duration and frequency of NCSE decreased significantly, nearly by half. This positive outcome was achieved through the combination of lacosamide 300 mg/day, valproate 2000 mg/day, and zonisamide 300 mg/day. In addition, cognitive evaluation revealed an improvement in reaction time, indicating a positive impact on cognitive function.

DISCUSSION

In this report, we present the case of a patient diagnosed with r(20) syndrome who exhibited drug-resistant NCSE and focal seizures with frightening visual hallucinations. However, with the introduction of lacosamide treatment, there was a significant reduction in both the frequency and intensity of these seizures. In addition, PET/CT imaging revealed hypometabolism in the frontal and parietal regions of the brain. These findings provide valuable insights into the potential therapeutic efficacy of lacosamide and the underlying neurobiological mechanisms associated with r(20) syndrome.

MAIN POINTS

- r(20) syndrome is characterized by non-convulsive status epilepticus attacks, long-lasting atypical absence seizures, and focal seizures with visual hallucinations.
- The specific diagnosis for r(20) chromosome is karyotyping.
- Electroencephalography and functional imaging studies suggest r(20) syndrome relates to frontal lobe network failure rather than a specific epileptogenic region.
- Lacosamide can be an alternative anti-seizure medication for non-convulsive status epilepticus related to the r(20) syndrome.

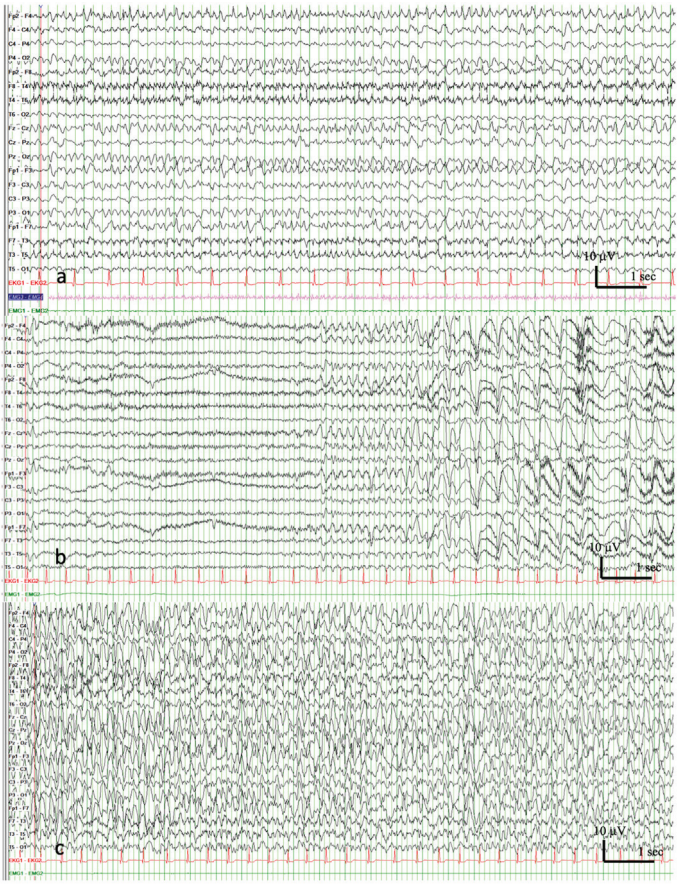

Figure 1. In electroencephalography (high pass filter 0.5 Hz, low pass filter 70 Hz, bipolar longitudinal montage). a) The sharply contoured theta activity prominent in the anterior part of the hemispheres interictally. b) Generalized 2.5 Hz spike and waves after evolution of 10-11 Hz fast rhythmic activity with the atypical absence seizure. c) Generalized 3-7 Hz fluctuating slow wave periods prominent in the anterior parts of the hemispheres, associated with the prolonged confusional state

Epidemiological Characteristics of r(20)

RCs are estimated to be in between 30,000 and 60,000 live births annually.[3] To date, there have been 200 documented cases of ring 20 chromosomes in the literature. In r(20) syndrome, the typical age of seizure onset is seven years.[2] In this study, the r(20) rate was 57%, and seizures started at the age of six years.

Seizure Types and Their Relationship to Mosaicism

In the literature, it has been observed that epilepsy in patients with ring chromosome 20 syndrome follows an age- and mosaicism-dependent course. The severity of cognitive impairment and the

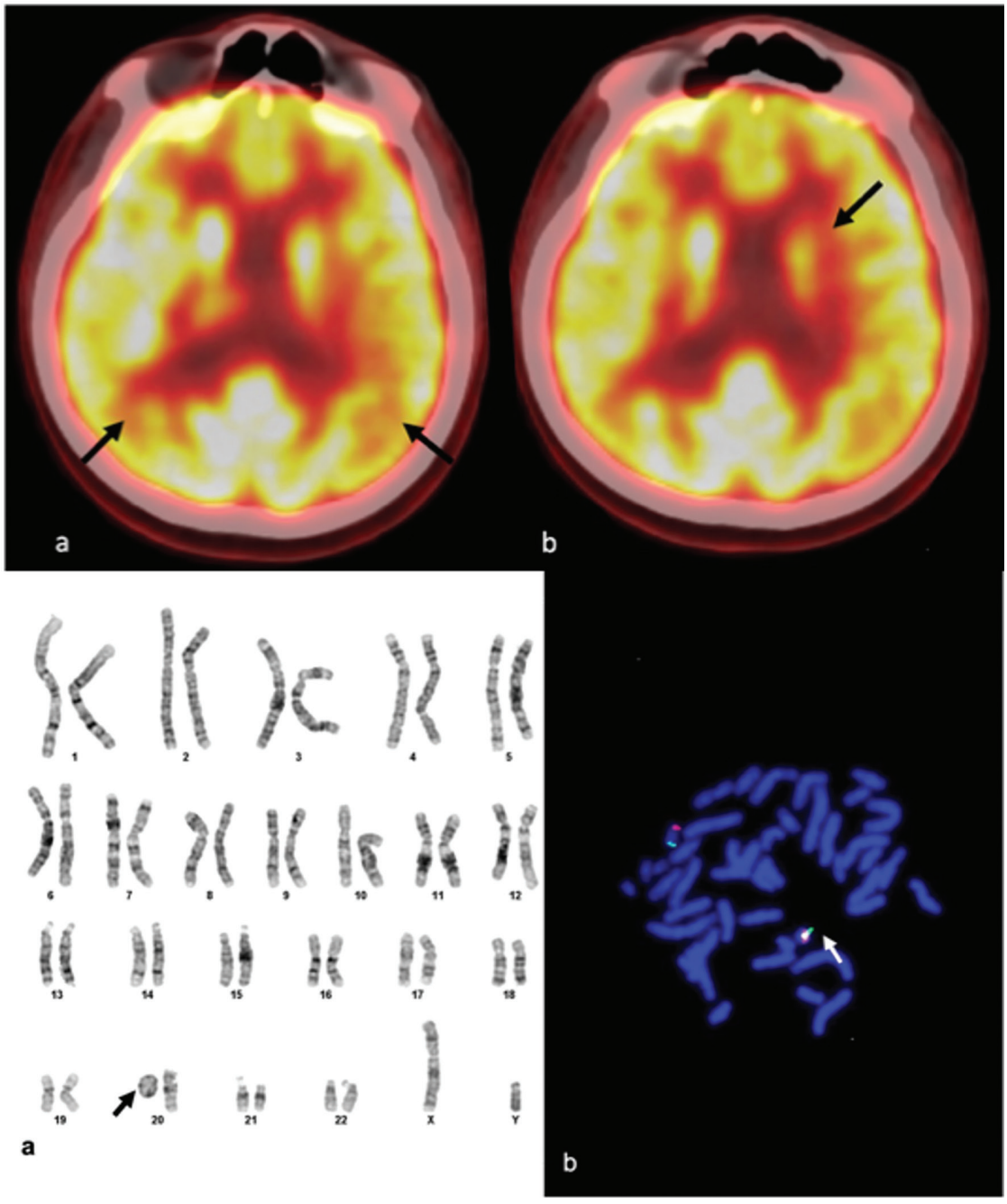

Figure 2. Upper image: a) Mild hypometabolism in the right and left parietal inferior, b) left prefrontal area in PET/CT examination (arrows).
Lower image: a) R(20) chromosome in karyotype analysis (black arrow) b) FISH image using a subtelomeric probe specific to the p and q arms of the 20th chromosome (white arrow)
PET/CT: Positron emission tomography/computed tomography

presence of r(20) mosaicism seem to be directly related, whereas they show an inverse correlation with the age of epilepsy onset. Non-mosaic patients tend to experience earlier seizures than mosaic patients.[2] In a study, the age at seizure onset was significantly lower in non-mosaic patients (median age of 2.1 years) than in mosaic patients (median age of 6.0 years). Furthermore, it was noted that males tend to develop epilepsy approximately 2 years earlier than females.[1,3]

When seizure onset occurs in childhood, patients often exhibit terrifying hallucinations along with focal motor seizures, which frequently occur during sleep. These prominent features can evolve into epileptic encephalopathy associated with NCSE. On the other hand, epilepsy onset during adolescence is often accompanied by a milder course without significant cognitive decline. Regrettably, less than 10% of patients achieve seizure freedom.[4] These findings demonstrate the complex and variable nature of ring chromosome 20 syndrome, with diverse clinical presentations and outcomes depending on patient age, mosaicism, and gender.

Our patient experienced nocturnal seizures characterized by waking up, staring, and mild tonic stiffening of the face and

extremities at the age of 6 years. These seizure manifestations align with the description of nocturnal hypermotor seizures in the literature.[3] During some of these episodes, the patient experienced terrifying hallucinations. It is worth noting that the sudden onset of fear during seizures and horrifying hallucinations were reported as early clinical signs, and in up to 25% of cases, they were evaluated as auras before the onset of the actual seizures.[5] This highlights the importance of recognizing these symptoms as they may provide valuable insights for early diagnosis and management of the condition.

NCSE is characterized by unresponsiveness, staring, confusion, and may include oral or motor automatisms, a frightened expression, and focal motor symptoms. These episodes comprise prolonged confusional states of varying intensity.[6] Our patient also exhibited periods of staring and decreased responsiveness, lasting up to 45 min and occurring daily. Some of these prolonged confusional states were accompanied by perioral myocloni. When evaluated using ictal EEG, these episodes were identified as another clinical feature of prolonged NCSE, distinguishable from those observed in idiopathic generalized epilepsy syndrome with perioral myoclonia. This distinctive presentation highlights the importance of careful evaluation and differentiation to accurately diagnose and manage the patient's condition.

EEG Findings

Interictal EEG typically shows slowed background activity and epileptic activity in the frontal lobes in r(20) syndrome. The focal epileptiform EEG findings observed since childhood in our patient indicated that visual hallucinations may be related to focal seizures. In our patient, we also observed interictal discharges with a frequency of 3-7 Hz in the anterior halves of the hemispheres, previously described as the "ring 20 rhythm".[6]

Pathophysiology

It has been suggested that the "primary visual cortex", the region where visual information is primarily processed, is responsible for "elementary" visual hallucinations, whereas "complex" visual hallucinations result from the inappropriate interpretation of perceptions due to dysfunction in the "Dorsal Attention Network" (DAN). The DAN consists of neural networks within the frontal eye areas, the dorsolateral prefrontal and posterior parietal cortex, and certain areas of the striatum.[7] Additionally, limbic structures are also activated due to the strong emotional components of complex visual hallucinations, as seen in our patient expressing immense fear after seeing the clown images.[8]

Interictal and ictal SPECT and PET/CT studies associated with ring 20 chromosome patients' seizures revealed a reduction in bilateral frontotemporal cortical perfusion and metabolism. In individuals with r(20) syndrome, Vaudano et al.[6] found cortical correlations between the blood oxygen level-dependent signal at bilateral sensory-motor and temporoparietal cortices and slow-wave activity. The decline in default mode network and DAN activity was more significant with higher manifestation of this slow-wave activity.[5] Group-level data analysis of interictal fMRI studies demonstrated the involvement of a complex frontal network, including the prefrontal, opercular-insular, and bilateral temporoparietal cortex in these seizures.[9]

Data obtained from EEG and hemodynamic imaging studies support the idea that r(20) syndrome is related to frontal lobe-associated network failure rather than a specific localized frontal cortical epileptogenic region.

Treatment

Although seizures in r(20) chromosome syndrome and NCSEs are typically drug resistant, some anti-seizure drugs such as valproate, lamotrigine, ezogabine, or their combinations have been reported to be beneficial in some individuals.[2] Lacosamide reduced the frequency of seizures by 50% in our patient, despite using many anti-seizure medications previously. Lacosamide treatment has been shown to reduce seizures, and this effect is attributed to the enhancement of the slow inactivation of voltage-gated sodium channels without affecting the fast component.[10,11]

CONCLUSION

The presence of the ring 20 chromosome anomaly should be considered when encountering patients with frequent and drug-resistant NCSE and early frightening hallucinations, as observed in our patient. These hallucinations may be associated with hypometabolism in the parietal and frontal brain regions, as detected on PET/CT imaging. Although seizures in this rare genetic disorder are typically treatment-resistant, lacosamide could be considered as an option to reduce the frequency of seizures in these cases. This highlights the importance of early recognition and appropriate management for improved outcomes in patients with ring 20 chromosome syndrome.

Ethics

Informed Consent: Written informed consent, including permission for publication, was obtained from the patient and his/her family.

Authorship Contributions

Surgical and Medical Practices: İ.İ.K., N.G.Ş., B.K., N.B., Concept: H.G., N.G.Ş., N.B., B.B., Design: H.G., İ.İ.K., T.K., B.B., Data Collection or Processing: H.G., İ.İ.K., T.K., N.G.Ş., Analysis or Interpretation: H.G., B.K., Literature Search: H.G., İ.İ.K., Writing: H.G., İ.İ.K., T.K., B.K., B.B.

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