Ring chromosome 20 and nonconvulsive status epilepticus
A new epileptic syndrome

Y. Inoue,¹ T. Fujiwara,¹ K. Matsuda,¹ H. Kubota,¹ M. Tanaka,¹ K. Yagi,¹ K. Yamamori¹ and Y. Takahashi²

¹National Epilepsy Center, Shizuoka Higashi Hospital, Shizuoka and ²Department of Pediatrics, Gifu University School of Medicine, Gifu, Japan
Correspondence to: Dr Yushi Inoue, National Epilepsy Center, Shizuoka Higashi Hospital, Urushiyama 886, Shizuoka 420, Japan

Summary
Six cases of epilepsy associated with ring chromosome 20 are presented. The study of these cases and 20 cases reported in the literature revealed that they constitute a distinct epileptic syndrome: frequent seizures consisting of a prolonged confusional state, with or without additional motor seizures, and an ictal EEG pattern of long-lasting bilateral paroxysmal high-voltage slow waves with occasional spikes. Neurological examination results were normal, and neuroimaging studies often failed to disclose a brain lesion. The seizures were resistant to antiepileptic drug therapy.

Comparison of the electroclinical features of nonconvulsive status epilepticus in six patients with and four patients without ring chromosome 20 revealed that the group with the chromosomal anomaly had more frequent, comparatively brief episodes of confusion associated with a less prominent spike component on the EEG. We propose that epilepsy associated with ring chromosome 20 constitutes a new syndrome that may provide an opportunity to scrutinize a genetic mechanism of epilepsy.

Keywords: chromosomal anomaly; ring chromosome 20; nonconvulsive status epilepticus; epileptic syndrome

Introduction
Ring chromosome 20 is a rare chromosomal anomaly. Only 23 cases have been reported in the literature. An association of ring chromosome 20 with epilepsy was first reported in 1972 (Atkins et al., 1972; Faed et al., 1972; de Grouchy et al., 1972; Uchida and Lin, 1972), and subsequent case reports disclosed that epilepsy constitutes the main clinical feature of this chromosomal defect. The presence of epileptic seizures was described in 21 of the 23 cases. One patient without seizures was 15 months of age at examination, which was too early to exclude the possible existence of epilepsy (Porfirio et al., 1987). Another case of ring chromosome 20 without seizures involved a phenotypically normal woman, a mother of two children with ring chromosome 20 associated with mental retardation, behavioural disorder and epilepsy (Back et al., 1989).

In spite of this frequent association of epilepsy, the clinical and EEG seizure descriptions failed to delineate a common epileptic feature in patients with ring chromosome 20, although the seizures were often intractable to medical therapy. We present six cases of ring chromosome 20 associated with epilepsy, one of which was reported previously (Takahashi et al., 1995). The study of these cases and a detailed review of the literature revealed that patients with epilepsy and ring chromosome 20 share many electroclinical features in common. We conclude that epilepsy associated with ring chromosome 20 constitutes a distinct syndromic entity.

Case reports
A chromosomal analysis of two patients (see Patients 1 and 2 below) was motivated by the presence of a family history...
of congenital heart disease in one and short stature in the other. These patients had nonconvulsive status epilepticus (NCSE), a condition characterized by prolonged clouding of consciousness accompanied by paroxysmal EEG activity and the discovery of ring chromosome 20 in them prompted us to examine the chromosomes of other patients presenting with NCSE prospectively. Of 40 patients with NCSE documented by intensive monitoring (simultaneous recording of seizures on closed-circuit television and the EEG) in our hospital, we examined eight patients who had been hospitalized for treatment in the last 12 months. All patients gave their written informed consent for this study, which was approved by the ethics committee of The National Epilepsy Center, Shizuoka. Electroclinical descriptions of previous seizures were available from the inpatient files.

Ring chromosome 20 was found in four of the eight patients. Detailed clinical descriptions of six patients with the chromosomal anomaly (Patients 1 and 2 plus these four patients) are followed by brief sketches of the four patients without the chromosomal anomaly in order to clarify the possible differences existing among them.

**Patients with ring chromosome 20**

**Patient 1**

This patient, a 14-year-old right-handed girl, had a maternal uncle who had died of heart disease soon after birth. A maternal cousin had a congenital heart anomaly. The patient developed normally.

At the age of 8 years she began to have seizures lasting 20–30 min, in which she looked dull and felt herself unclear. Consciousness was disturbed with varying severity. Afterwards, she could recall her activity during the mild clouding of consciousness that had occurred. This seizure occurred two or three times daily. Occasionally she experienced hallucinations of children or wolves appearing at the beginning of the seizure. The maximum duration of the seizure was 90 min. The longest seizure-free interval was 10 days, when she suffered from pneumonia.

She also had another type of seizure in which her conversation and behaviour slowed, her activity stopped, and she opened her eyes and stared. Turning of the head to the left was sometimes observed. This seizure stopped within 1 min, and occurred during the prolonged episode of clouding of consciousness as well as in sleep. She had two generalized convulsions preceded by versive movements of the head and eyes to the left when the medication was reduced during treatment in hospital.

The interictal EEG showed an 8–10-Hz alpha wave rhythm with frequent right anterior-dominant 4–5-Hz waves with spikes. The ictal EEG showed 10–25-Hz recruiting spike activity followed by 2–3-Hz generalized high-voltage slow waves with spikes during the brief staring seizure. During the prolonged confusional episode, spike activity appeared in the right frontal region and was followed by high-voltage slow waves with spikes that gradually fragmented (Fig. 1). Intravenous diazepam injection stopped the discharge. On magnetoencephalography (MEG), spike dipoles were not localized but were scattered over both frontal lobes.

There were no abnormal findings on MRI and no abnormal regional perfusion on single photon emission computerized tomography (SPECT). On the revised Wechsler intelligence scale for children (WISC-R), she scored an IQ of 81 (verbal IQ, 79; performance IQ, 87). She showed no behavioural disorders. Low achievement on fluency tests and the Wisconsin card sorting test (WCST) suggested reduced frontal lobe function. School performance decreased after the appearance of the frequent seizures. The seizures were resistant to antiepileptic drug therapy.

Cytogenetic studies carried out on PHA (phytohaemaglutinin)-stimulated blood lymphocytes stained with trypsin-Giemsa banding technique showed the presence of ring chromosome in 20% of the lymphocytes studied: 46,XX,r(20)(p13q13.33)[4]/46,XX[16].

**Patient 2**

This patient, a 13-year-old boy, has been described elsewhere (Takahashi et al., 1995). So the electroclinical features of his epilepsy are only briefly summarized here. Epilepsy began at the age of 3 years and 4 months. The seizure occurred several times a week, during both sleep and wakefulness, and was easily precipitated by playing video games. The seizure consisted of an abrupt utterance of meaninglessness words, shaking of the arms and legs, and vigorous movements with his face flushed. When the seizure occurred in the awake state, it was often preceded, or followed by, a state of fluctuating consciousness accompanied by myoclonias of the eyelids and extremities, and restless behaviour lasting 10–15 min.

The interictal EEG showed bilateral asynchronous spikes or polyspikes followed by high-amplitude slow waves in the frontopolar and frontal regions. The ictal EEGs were characterized by the initial appearance of delta waves in the frontopolar regions followed by a burst of diffuse high-amplitude delta waves, which were then replaced by a run of low-amplitude fast activity. The delta waves lasted as long as 15 min. SPECT showed decreased perfusion in the right frontopolar region interictally, and MRI suggested the presence of cortical dysplasia.

The patient displayed restless and impulsive behaviour. He was of short stature, and an endocrinological examination suggested partial growth hormone deficiency due to hypothalamic dysfunction. The IQ (WISC-R) was 59 (verbal IQ, 51; performance IQ, 59). Ring chromosome 20 was present in 53% of the lymphocytes studied: 46,XY,r(20)(p13q13.33)[16]/46,XY[14].

**Patient 3**

This patient, a 21-year-old right-handed woman, had maternal grandparents who were consanguineous. There was...
Fig. 1 An ictal EEG from Patient 1. Repetitive spikes occurred in the right frontal region and were then followed by 3-4-Hz slow waves and frontal-dominant bilateral 3-Hz spike-and-wave complexes. Spike-and-wave complexes gradually lost the spike component with increasing frequency and became polymorphous. The seizure lasted 39 min, and the breaks between these records are 300, 450, 480, 660, 300 and 105 s long. Verbal response was impaired to various degrees, ranging from simple slowness, perseveration and inappropriate utterance to muteness.

no family history of epilepsy or major anomalies. After an uncomplicated birth, she developed normally. She graduated from high school and then learned computer technology. At the age of 14 years, she began to have episodes of clouding of consciousness lasting 10–50 min. Her behaviour suddenly slowed and became disordered, and she sometimes walked aimlessly around. She responded inappropriately, and sometimes became mute. She usually fell asleep at the end of the episode. The episode occurred one to three times daily. Treatment with various antiepileptic drugs completely failed to influence the episodes. She visited our hospital at the age of 21 years. She never experienced other types of seizures or other behavioural problems. She was normal neurologically, and had no dysmorphic features.

The EEG showed fairly organized 9-Hz background activity with abundant intermittent irregular high-voltage slow waves.
An ictal EEG from Patient 3. Frontal-dominant irregular high-voltage slow waves with occasional spikes lasted 40 min. The patient looked indifferent and weary. Verbal responses were short and often inappropriate. Complex mental action such as calculation or thinking was impossible. She went to sleep near the end of the discharge.

or sharp waves interictally. The ictal EEG revealed continuous high-voltage slow waves with occasional spikes over both hemispheres (Fig. 2). The ictal MEG showed localized clustering of spike dipoles on the anterior medial surface of the frontal lobe. MRI disclosed several small spots with a high T2-weighted signal in the subcortical layer of the right frontal lobe. SPECT revealed ictal hyperfusion of the right frontal lobe. She performed normally on the WCST and fluency tests, and her IQ was 81 on the Wechsler adult intelligence scale—revised (WAIS-R; verbal IQ, 77; performance IQ, 95). Ring chromosome 20 was found in 25% of the lymphocytes studied: 46,XX,r(20)(p13q13.33)[5]/46,XX[15].

![Fig. 2 An ictal EEG from Patient 3. Frontal-dominant irregular high-voltage slow waves with occasional spikes lasted 40 min. The patient looked indifferent and weary. Verbal responses were short and often inappropriate. Complex mental action such as calculation or thinking was impossible. She went to sleep near the end of the discharge.](image-url)
**Patient 4**

This patient, a 28-year-old right-handed woman, had no relevant family history. She developed normally until 7 years of age when the seizures started. At the age of 3 years 9 months, she slipped on some steps and received a blow to the left front of her head. Shortly thereafter she had a convulsive seizure with fever and vomiting, which was repeated once more 2 h later. Various examinations, including EEG, revealed normal findings.

She graduated from a special high school for handicapped students, and was working in a sheltered workshop. It was difficult for her to establish smooth interpersonal relationships because of her inattentive and selfish behaviour. She visited our hospital at the age of 15 years because the seizures had not improved despite medical management since their first onset at 7 years of age. She had two types of seizures, both of which occurred daily. One involved complex motor automatisms lasting 1–2 min, which consisted of increased tonicity, downward retraction of the corners of the mouth, eye opening and fearful action with utterances. The ictal EEG showed 6-Hz rhythmic activity followed by desynchronization and theta wave rhythm. The other seizure type was episodes of fluctuating consciousness lasting 20–30 min. The ictal EEG showed bursts of diffuse high-voltage slow waves or spike-and-wave complexes (Fig. 3). The interictal EEG showed bilateral diffuse high-voltage slow waves or spike-and-wave complexes and bilateral frontal spikes.

Neurologically she was normal. The IQ (WAIS-R) was 47 (verbal IQ, 54; performance IQ, 56), indicating a retarded mental state. There was no abnormal finding on the MRI, but SPECT showed decreased perfusion of the right frontotemporal region interictally. The seizures were extremely difficult to control with antiepileptic drugs. Ring chromosome 20 was found in 40% of the lymphocytes studied: 46,XX,r(20)(p13q13.3)[13]/46,XX[12].

**Patient 5**

This patient, a 31-year-old right-handed woman, had no relevant family or personal history. She graduated from high school and was working in spite of frequent seizures. The seizures, which started at the age of 7 years, lasted 5–30 min, or occasionally 90–120 min. The attacks had increased gradually and occurred daily since the age of 20 years. She felt tired at the beginning of the seizure and looked drowsy and dull, showing an apathetic facial expression, and she became mute. She did not become totally unconscious but could continue foregoing activity. The seizures occurred predominantly in the evening. Maximum freedom from seizures was only 1 day.

Hyperventilation easily induced the seizure. The interictal EEG showed bilateral high-voltage slow waves over the frontal area. The ictal EEG indicated bilateral, almost synchronous, high-voltage slow wave bursts with occasional spikes predominantly over the frontal area (Fig. 4). The frequency of discharge changed during the ictus. MEG revealed a wide clustering of spike dipoles in the middle part of the right hemisphere, including the insular region. Intravenous injection of lidocaine stopped the seizure. Zonisamide reduced the seizure slightly, but other antiepileptic drugs did not influence the seizures. She had no other types of seizures. The results of blood tests, including hormone tests, were normal. There was no abnormal finding on MRI, but SPECT showed interictal hypoperfusion and ictal hyperperfusion of the right frontotemporal region. The IQ on the WAIS-R was 95 (verbal IQ, 81; performance IQ, 116). The results of the WCST and fluency tests were normal. Cytogenetic studies showed the anomaly of chromosome 20: 46,XX,r(20)(p13q13.3)[13]/47,XX,+20[1]/46,XX[36].

**Patient 6**

This patient, a 25-year-old right-handed man, had no relevant family or personal history. He graduated from high school and qualified as a social worker. At the age of 11 years, he began to have seizures. His activities stopped or became slow and inappropriate, and he was mute for several min. He was amnestic for the episode. The seizure then became frequent and began to last longer. At the age of 21 years, when he first visited our hospital, the seizures occurred almost daily and were of 15–60 min duration. He was not totally unresponsive, and could obey simple commands slowly. Sometimes brief episodes of eyes turning upwards or to the left occurred at the onset of or during the prolonged clouding of consciousness. In addition, he had convulsive seizures once a month, mainly during sleep. Turning of the eyes and head to the left was accompanied by a twitching movement of the left corner of his mouth, and then generalized convulsions developed. Paresis of the left extremities and deviation of the eyes to the right were observed postictally. The seizures were medically intractable.

The EEG consisted of abundant spikes, spike-and-wave complexes, or slow activity over the right anterior frontal and temporal regions. The ictal EEG started in the right anterior frontal area with recruiting spike activity which then evolved to prolonged high-voltage slow waves or spike-and-wave complexes (Fig. 5). MEG disclosed a cluster of spike dipoles in the frontopolar and anterior basal frontal regions on the right side and occasionally in the left temporal area. Neuroimaging studies (CT, MRI and SPECT) showed no lateralized or localized findings. Neuropsychological examinations revealed an IQ of 74 on the WAIS-R (verbal IQ, 74; performance IQ, 83), normal achievement on the WCST, and reduced verbal fluency. He was neurologically normal and displayed no dysmorphic features.

Because of the intractable seizures, he had an intracranial EEG study. Ictal subdural EEG recording strongly suggested that the seizure originated in the right anterior basal frontal region (Fig. 6). Anterior frontal corticectomy was performed on the right side, and the seizure was reduced considerably.
Fig. 3 An ictal EEG from Patient 4. Prolonged continuation of irregular high-voltage slow waves occurred with occasional spikes. During the seizure she looked absent, and could not answer questions or obey commands until 2–3 min before the end of the discharge. She always reacted to external stimuli such as pain. The seizure lasted 31 min.

On the postoperative EEG, reduced spike activity was found in the left frontotemporal region.

Ring chromosome 20 was present in 10% of the lymphocytes studied: 46,XY,r(20)(p13q33)[3]/46,XY[27].

**Patients without ring chromosome 20**

**Patient 7**

This patient, a 48-year-old right-handed woman, had no relevant family or personal history. Since the age of 15 years, she had generalized convulsions preceded by clonic jerks of the right arm and turning of the head and trunk to the right, which occurred yearly. Paresis of the right extremities was observed in the postictal phase. Another type of seizure, characterized by prolonged impairment of consciousness, ranging from 3 min to 4 h, began to occur several times a month from the age of 26 years. During these episodes, the patient was mute and dull.

At the beginning of the confusion, isolated spikes, higher in amplitude on the left side than on the right, appeared in the frontocentral region and were followed by bilateral diffuse spike-and-wave discharges ranging from 2 to 2.5 Hz (Fig. 7A). The prolonged state of confusion was occasionally replaced by sudden versive movements of the head and trunk with clonic jerks of the right arm accompanied by fast EEG activity of about 13 Hz. MEG spikes corresponding to the EEG spike-and-wave complexes were observed only in the left frontal lobe, not on the right side. Dipoles did not cluster but were distributed over the left frontal lobe. MRI showed slight perirolandic atrophy on the left side. SPECT revealed interictal hypoperfusion of the left frontal region, which reversed into hyperperfusion of the same area ictally. The IQ was 80 on the WAIS-R (verbal IQ, 77; performance IQ, 88).

**Patient 8**

The patient, a 30-year-old right-handed woman, had no relevant family or personal history. Convulsive seizures began at the age of 11 years, and prolonged nonconvulsive seizures at 14 years, which occurred one to three times a month.

During the nonconvulsive seizures, which lasted from hours to several days, mild and fluctuating clouding of consciousness was observed. Occasionally, brief motor seizures, with rhythmic versive movements of the head and
Fig. 4 An ictal EEG from Patient 5. The ictal discharge began with a frontal dominant slow-wave rhythm that gradually became larger in amplitude. The slow waves were occasionally accompanied by spikes. The frequency of the discharges often changed. The seizure lasted 26 min. The patient’s mental state fluctuated. She could sometimes follow commands such as ‘open your eyes’ or ‘raise your hands’, but most of the time she could not. Occasionally, she could respond verbally, but only to simple questions such as those concerning her personal profile. She was mute and motionless when high-voltage slow waves became faster or were accompanied by spikes.

eyes toward the right and with phonation, interrupted the confusional state.

The interictal EEG showed spikes or polyspikes in the left frontal region. Ictal spike discharges appeared in the left frontal region and were followed by diffuse 3–4 Hz spike-or polyspike-and-wave complexes with occasional sharp-wave bursts (Fig. 7B). The MRI was normal. She scored an IQ of 104 on the WAIS-R (verbal IQ, 96; performance IQ, 116).

Patient 9

The patient, a 42-year-old right-handed woman, had no relevant family or personal history. Epilepsy began at the age of 18 years with a generalized convolution, and NCSE appeared at the age 20 years. Epileptic status with fluctuating clouding of consciousness and perseverative or automatic behaviour lasted from hours to 3 days and occurred once a month. Versive convulsive seizures toward the right, with or without secondary generalization, were occasionally simultaneous with or followed by the confusional state. Paresis of the right arm was observed after the convulsive seizure.

An interictal EEG showed focal spikes or spike-and-wave complexes in the left frontal lobe. Ictally, a run of polyspike-and-wave complexes at ~2 Hz appeared unilaterally in the left frontal region which was then followed by a bilateral 2-Hz polyspike-and-wave rhythm with higher amplitude in the left frontal region than in the right (Fig. 7C). MEG spike dipoles clustered over the peri-insular region on the left side. The MRI was normal.
Patient 10
The patient, a 35-year-old right-handed woman, had brief absence seizures with myoclonias of the eyelids and arms since the age of 4 years. At the age of 11 years, absence status appeared. These prolonged seizures lasted from several hours to 2 days and occurred once or twice a month. There was marked clouding of consciousness with mutism. The seizure frequency decreased with age, and recently the frequency was two to three times a year. The EEG showed diffuse spike-and-wave complexes interictally and prolonged 3–5-Hz spike- or polyspike-and-wave complexes during the absence status (Fig. 7D). The CT was normal.
Fig. 6 An ictal subdural EEG recording from Patient 6. Only the initial part of the prolonged discharge is shown. The ictal discharge started at C1–3 and D1–3 (right anterior frontal region) in the form of a fast small-spike rhythm which then spread posteriorly, accompanied by slow waves. Spike-and-wave complexes were maximum in amplitude in the anterior frontal region on the right side.

Fig. 7 Parts of prolonged ictal EEGs from Patient 7 (A), Patient 8 (B), Patient 9 (C) and Patient 10 (D). The EEGs were characterized by the repetition of spike- or polyspike-and-wave complexes.
Discussion of cases

Characteristics of seizures in patients with ring chromosome 20

The seizures in our six patients with ring chromosome 20 (Patients 1–6) had the following features in common:

(i) The seizures consisted of a prolonged confusional state in all patients, and brief motor seizures or convulsions also occurred in four of the six patients. Clouding of consciousness was fluctuating and not so severe as to cause total unresponsiveness or motionlessness. An expressionless face, muteness, inattentiveness, perseveration, and slowness of response and behaviour were observed. Patients could recall the events occurring during their mild confusion. The duration of the seizure was usually 10–50 min, which is longer than the usual epileptic seizure, although it rarely exceeded 60 min. Seizures occurred daily or at least weekly in all patients. These prolonged and frequent seizures often impaired the patients’ daily life.

(ii) The ictal EEG showed long-lasting high-voltage slow waves with occasional spikes, which sometimes localized to a unilateral, usually frontal, region, but they easily became bilateral. The frequency often changed. Spike-and-wave complexes were never the predominant EEG feature.

(iii) MEG suggested a localized or lateralized origin for the spikes in three patients, and SPECT showed decreased regional perfusion in three patients interictally and increased regional perfusion in two patients ictally.

(iv) Neurological and MRI findings were normal except in Patients 2 and 3, in whom it was uncertain whether the MRI finding was relevant to the occurrence of seizures. Significant personal antecedents were not found in any patient except Patient 4.

(v) The seizures were refractory to the antiepileptic drug therapy in all patients.

Additional motor seizures were observed in four patients, with eye or head turning in two (Patients 1 and 6), complex motor automatisms in two (Patients 2 and 4), and generalized convulsions preceded by versive movements of the head and eyes in two (Patients 1 and 6). In these four patients, EEG or MEG or SPECT showed lateralizing or localizing signs suggesting a focal nature of the epileptogenesis. In the remaining two patients (Patients 3 and 5) who exhibited only a confusional state as an ictal event, MEG or SPECT showed lateralized signs. The epileptogenic nature of these two cases, therefore, may well be focal too.

NCSE presents in two forms: generalized (absence status epilepticus) and partial (complex partial status epilepticus) (Gastaut, 1983), and a considerable proportion of NCSE is reported to be of the latter type (Tomson et al., 1986; Kudo et al., 1995). According to the electroclinical features, our cases appear to belong to the category of complex partial status epilepticus.

Comparative analysis

The electroclinical findings in the patients with and without ring chromosome 20 are summarized in Tables 1 and 2, respectively. Although the sample size is small, seizures in patients with the chromosomal anomaly tended to be more frequent, often occurring daily, and shorter than those of patients without the chromosomal anomaly, often resolving within 1 h. The EEGs showed high-voltage slow waves with occasional spikes in the patients with ring chromosome 20, whereas in the patients without the anomaly the spike component was more prominent. The onset of NCSE in patients with the chromosomal anomaly often coincided with the onset of epilepsy, while patients without the anomaly often had isolated convulsive or nonconvulsive seizures before the onset of prolonged seizures. Other electroclinical features did not seem to differ significantly in this small sample.

Review of the literature

There were 20 cases of epilepsy and ring chromosome 20 reported previously by other authors (Table 3). The electroclinical features of the 26 cases, including our six cases, can be summarized as follows: there were 14 females and 11 males, sex was not mentioned in one case. Age at examination ranged from 6 months to 31 years. Age at seizure onset ranged from 1 day to 14 years (mean 4.5 years). One patient died at age 7 months (de Grouchy et al., 1972). There was only one report in which the seizures responded to medical therapy (Lancman et al., 1993), but others noted refractoriness to antiepileptic medication (21 cases). Neuroimaging studies have revealed no abnormal findings so far, except for our Patients 2 and 3. Frequent seizure occurrence, often daily, was mentioned in 14 cases. Prolonged electroclinical seizures were described in 15 cases. When described, the seizure duration was often ≤60 min. In 17 cases, either frequent seizures or a prolonged electroclinical seizure pattern, or both, were described. Minor motor seizures or convulsions were often described in addition to the prolonged seizures.

There was often mosaicism in the reports of ring chromosome 20. The percentage of r(20) in lymphocytes varied from 10% to 100% (mentioned in 20 cases). The locus of ring formation was pl3ql3, pl3ql3.3 or pl3ql3.33 in the 12 cases mentioned.

The main features of the epilepsy presented by patients with ring chromosome 20 are thus frequent and prolonged seizures and therapy resistance.

Characterization of the epilepsy–ring chromosome 20 syndrome

NCSE with a prolonged confusional state of varying severity and with continuous diffuse paroxysmal EEG activity is a rare condition. Fujiwara et al. (1988) compared the electroclinical characteristics of absence status in 14 children and 14 adults. They found that the absence status in adults tended to show more focal electroclinical features, less profound clouding of
Table 1  
Electrophysiology and clinical data in patients with epilepsy and ring chromosome 20

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age/age at epilepsy onset (years)</th>
<th>Seizure characteristics</th>
<th>Interictal EEG features</th>
<th>Ictal EEG features</th>
<th>MEG</th>
<th>MRI</th>
<th>SPECT</th>
<th>Psychology/behaviour</th>
<th>Chromosome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>14/8</td>
<td>Confusional state lasting 20–30 min (2–3 times daily); brief CPS and staring (several per day); 2 GTCs</td>
<td>R-frontal dominant spikes, spike–waves</td>
<td>R-frontal spike activity followed by prolonged high-voltage slow waves with spikes; recruiting spike activity followed by bilateral high-voltage slow waves with spikes</td>
<td>Spike dipoles bilaterally posterior–inferior frontal</td>
<td>Normal</td>
<td>No localized findings</td>
<td>IQ = 81</td>
<td>r(20)pl13q13.33 20%</td>
</tr>
<tr>
<td>2†</td>
<td>M</td>
<td>13/3</td>
<td>Prolonged episode of myoclonias of eyelid and extremities and confusion preceded or followed by complex motor automatisms (several per week)</td>
<td>Bilateral asynchronous spike/polyspikes followed by high-amplitude slow waves in frontal</td>
<td>High-amplitude 8 waves (lasting &gt;10 min) followed by a min of low-amplitude fast activity</td>
<td>Not done</td>
<td>L-frontal lesion</td>
<td>Intercital R-frontal hyper-perfusion</td>
<td>IQ = 59; restless, impulsive behaviour</td>
<td>r(20)pl13q13.33 53%</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>21/14</td>
<td>Confusional state lasting 10–50 min (1–3 times daily)</td>
<td>Irregular high-voltage slow waves or sharp waves</td>
<td>Bilateral high-voltage slow waves with occasional spikes</td>
<td>Spike-dipole cluster, anteromedial frontal</td>
<td>R-frontal small lesions</td>
<td>Intercital R-frontal hyper-perfusion</td>
<td>IQ = 81</td>
<td>r(20)pl13q13.33 25%</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>28/7</td>
<td>Confusional state lasting 20–30 min (several per day); complex motor automatisms (several per day)</td>
<td>Bilateral diffuse high-voltage slow waves or spike–waves; bilateral frontal spikes</td>
<td>Burst of diffuse high-voltage slow waves or spike–waves; 6-Hz rhythm followed by desynchronization and 8 waves</td>
<td>Not done</td>
<td>Normal</td>
<td>Intercital hypoperfusion R-frontal-T</td>
<td>IQ = 47; inattentive and selfish behaviour</td>
<td>r(20)pl13q13.33 40%</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>31/7</td>
<td>Confusional state lasting 5–30 min (several per day)</td>
<td>Bilateral frontal dominant 4–6-Hz high-voltage slow waves</td>
<td>Bilateral, almost synchronous high-voltage slow waves with occasional spikes</td>
<td>Spike-dipole cluster around the right insular region</td>
<td>Normal</td>
<td>R-frontal-T hypo/hyper perfusion interictally/ictically</td>
<td>IQ = 95</td>
<td>r(20)pl13q13.3 26%</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>25/11</td>
<td>Confusional state lasting 15–60 min accompanied by eye turning (several per day); GTC (monthly)</td>
<td>Spikes, spike–waves or slow waves dominant R-frontally; L/T spikes</td>
<td>R-frontal recruiting spike activity, evolving to prolonged bilateral high-voltage slow waves or spike–waves</td>
<td>R-anterobasal frontal and L/T spike–dipole cluster</td>
<td>Normal</td>
<td>No localized findings interictally or interictically</td>
<td>IQ = 74</td>
<td>r(20)pl13q13.33 10%</td>
</tr>
</tbody>
</table>

| F = female; M = male; L = left; R = right; T = temporal; CPS = complex partial seizure; GTC = generalized tonic–clonic seizure. *Chromosome studied in lymphocytes; percentage indicates the proportion of r(20) mosaicism. †Reported previously by Takahashi et al. (1995). |

Table 2  
Electrophysiology and clinical data in patients with epilepsy and without ring chromosome 20

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at seizure onset (years)</th>
<th>Age at NCSE onset (years)</th>
<th>Seizure characteristics</th>
<th>Interictal EEG features</th>
<th>Ictal EEG features</th>
<th>MEG</th>
<th>MRI</th>
<th>SPECT</th>
<th>Psychology/behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>F</td>
<td>48/15</td>
<td>26</td>
<td>GTC beginning on R; prolonged confusion up to 4 h terminated by motor seizure (monthly)</td>
<td>Bilateral spike–waves, L-frontal localized spike–waves</td>
<td>L-frontal-C recruiting spikes, then bilateral spike–waves</td>
<td>L-frontal spike dipoles</td>
<td>Normal</td>
<td>Normal</td>
<td>L-frontal hypo/hyper perfusion interictally/ictically</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>30/11</td>
<td>14</td>
<td>GTC, prolonged confusion up to several days (monthly) with occasional versive motor seizure</td>
<td>L-frontal spikes or polyspikes</td>
<td>L-frontal spikes followed by diffuse spike/polyspike–waves</td>
<td>Not done</td>
<td>Normal</td>
<td>Not done</td>
<td>IQ = 104</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>42/18</td>
<td>20</td>
<td>GTC; prolonged confusion up to 3 days (monthly) with occasional versive seizure</td>
<td>L-frontal spikes or spike–waves</td>
<td>L-frontal polyspikes followed by diffuse polyspike–waves</td>
<td>Not done</td>
<td>Normal</td>
<td>Not done</td>
<td>Not tested</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>35/4</td>
<td>11</td>
<td>Absence with myoclonias; absence status lasting up to 2 days (monthly)</td>
<td>Diffuse spike–waves</td>
<td>Diffuse bilateral spike– or polyspike–waves</td>
<td>Not done</td>
<td>(CT) normal</td>
<td>Not done</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

NCSE = nonconvulsive status epilepticus; C = central; for other abbreviations, see Table 1.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Onset age (years)</th>
<th>Seizure characteristics</th>
<th>EEG features</th>
<th>Chromosome (lymphocytes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uchida et al. (1972)</td>
<td>F</td>
<td>23</td>
<td>10</td>
<td>Petit mal, a series of grand mal seizures</td>
<td>Typical seizure pattern</td>
<td>r(20), 22%</td>
</tr>
<tr>
<td>de Grouchy et al. (1972)</td>
<td>M</td>
<td>6 months</td>
<td>3 months</td>
<td>Seizure (died at 7 months)</td>
<td>Not mentioned</td>
<td>r(20), 100%</td>
</tr>
<tr>
<td>Atkins et al. (1972)</td>
<td>M</td>
<td>7</td>
<td>6</td>
<td>Grand mal (4–6 times daily on admission)</td>
<td>Continuous sharp and multiple spikes and slow wave complexes in both hemispheres</td>
<td>r(20), 94%</td>
</tr>
<tr>
<td>Fae d et al. (1972)</td>
<td>M</td>
<td>11</td>
<td>4</td>
<td>Episodes of mood abnormality and automatic behavior accompanied by varying degrees of alteration of consciousness; minor seizures with twitching of the upper limbs</td>
<td>Extensive bilateral abnormality</td>
<td>r(20), 60%</td>
</tr>
<tr>
<td>Herva et al. (1977)</td>
<td>F</td>
<td>21</td>
<td>5</td>
<td>Epileptic seizure</td>
<td>Extensive bilateral abnormality and pronounced seizure activity,predominantly R-O,T</td>
<td>r(20)</td>
</tr>
<tr>
<td>Jalbert et al. (1977)</td>
<td>F</td>
<td>10</td>
<td>4</td>
<td>Absence-like episode (varying duration) accompanied by fear expression; confusional episode lasting up to 30 min; frequent brief seizures with crying and anxious expression occurring in sleep</td>
<td>L-T abnormality or bifrontal spike–wave paroxysm; frequent bilateral paroxysms with anterior dominance</td>
<td>r(20), 56%</td>
</tr>
<tr>
<td>Jacobs et al. (1978)</td>
<td>M</td>
<td>27</td>
<td>18 months</td>
<td>Seizure</td>
<td>Not mentioned</td>
<td>r(20)p13q13.3, 100%</td>
</tr>
<tr>
<td>Stewart et al. (1979)</td>
<td>M</td>
<td>2</td>
<td>12 months</td>
<td>Episode lasting 30 min with head turning to left and eye glazing; 20 s spells with mounting movements and twitching of the R arm and leg followed by excitement: up to 5 times daily</td>
<td>Occasional paroxysmal features without clear lateralization</td>
<td>r(20), 87.5%</td>
</tr>
<tr>
<td>Burnell et al. (1985)</td>
<td>F</td>
<td>5</td>
<td>3 days</td>
<td>Generalized seizure at day 3; episodes of sudden inappropriate giggling followed by limpness, unresponsiveness and frothing at the mouth</td>
<td>Normal</td>
<td>r(20),100%</td>
</tr>
<tr>
<td>Back et al. (1989) case 1</td>
<td>M</td>
<td>15</td>
<td>23 months</td>
<td>GTC during sleep (2–3/week); frequent CPS with blinking, fixated stare and verbal automation with crescendo–decrescendo character; epileptic twilight state and ictus over several days</td>
<td>Interictal bilateral spike–wave patterns; ictal irregular spike–wave discharges (R–C, T)</td>
<td>r(20), 87.5%</td>
</tr>
<tr>
<td>Back et al. (1989) case 2</td>
<td>F</td>
<td>16</td>
<td>2</td>
<td>Myoclonia; sporadic petit mal; occasional GTC; temporary inability to speak, nervousness and anxiety; daily CPS lasting up to 30 min.</td>
<td>Interictal bilateral, especially hifrontal, spike–wave patterns; R–C,T ictal accentuation of irregular spike–waves (CPS), progressing to generalization</td>
<td>r(20), 66.6%</td>
</tr>
<tr>
<td>Thomsen et al. (1989)</td>
<td>F</td>
<td>4</td>
<td>2 days</td>
<td>Febrile and afebrile convulsions with grimacing, upward rolling of the eyeballs and postictal drowsiness</td>
<td>Normal</td>
<td>r(20)p13q13.3, 87%</td>
</tr>
<tr>
<td>Dubeau et al. (1991)</td>
<td>F</td>
<td>15</td>
<td></td>
<td>Seizure</td>
<td>Not mentioned</td>
<td>r(20)p13q13.3, 100%</td>
</tr>
<tr>
<td>Halal et al. (1992)</td>
<td>M</td>
<td>14</td>
<td>8</td>
<td>Absence episode lasting 2 min occurring every 10 days</td>
<td>Slow and sharp irregularity with intermittent sharp slow waves over the R-frontal, C, T region</td>
<td>r(20)p13q13.3, 100%</td>
</tr>
<tr>
<td>Parisi et al. (1993)</td>
<td>F</td>
<td>6</td>
<td>5 months</td>
<td>Convulsion, loss of consciousness episode preceded by eye opening and fear sensation</td>
<td>Bilateral frontal rhythmic spikes and spike–waves</td>
<td>r(20)</td>
</tr>
<tr>
<td>Lancman et al. (1993)</td>
<td>M</td>
<td>15</td>
<td>1 day</td>
<td>Tonic seizure, later associated with a clonic component (monthly); staring spells</td>
<td>Moderate–severely generalized slowing, with generalized spike–wave discharges almost continuously</td>
<td>r(20)</td>
</tr>
<tr>
<td>Holopainen et al. (1994)</td>
<td>F</td>
<td>11</td>
<td>7</td>
<td>Short, infrequent absence-type attacks increasing in frequency and duration over the years, prolonged confusion–absence paroxysm at 10 years</td>
<td>Abundant focal epileptiform activity (R-frontal,T region) bilateral spike–wave discharges almost continuously</td>
<td>r(20)p3q13, 20%</td>
</tr>
<tr>
<td>Fukushige et al. (1995)</td>
<td>?</td>
<td>27 months</td>
<td>1</td>
<td>Daily seizure with fixation of eyes and flexion of arms, eyelid clonia, generalized/L-hemiconvulsion</td>
<td>Focal spike–waves</td>
<td>r(20)p13q13.3, 87%</td>
</tr>
<tr>
<td>Yamadera et al. (1996)</td>
<td>F</td>
<td>22</td>
<td>3</td>
<td>Loss of consciousness for 20 min, oral automatism, status epilepticus for 2 months, tonic seizure and clonic seizure</td>
<td>Moderate–high voltage bilateral 2–3 Hz δ waves with sharp waves</td>
<td>r(20)p13q13.3, 87%</td>
</tr>
<tr>
<td>Kobayashi et al. (1996)</td>
<td>M</td>
<td>23</td>
<td>7</td>
<td>Impaired consciousness with automatism, tonic seizure, status epilepticus, episode of hallucination, mute and violence</td>
<td>Long-lasting 3–5 Hz θ waves or spike–wave rhythm with changing frequency over frontal area which easily generalized; repetitive 5–6 Hz sharp waves</td>
<td>r(20)</td>
</tr>
</tbody>
</table>

O = occipital; C = central; for other abbreviations, see Table 1.
consciousness and more resistance to therapy than in children. Children with absence status often experienced individual absence seizures and an evolution of absences into absence status. Features of patients with ring chromosome 20 seem to be associated with adult absence status.

However, the comparison of clinical features between patients with and without ring chromosome 20 suggests, the frequent occurrence and short duration of clouding of consciousness (<60 min) in patients with ring chromosome 20 do not constitute the typical feature of adult NCSE. Granner and Lee (1994) reported that most of their 78 patients with NCSE experienced a single episode of NCSE. Regarding the duration of NCSE, there are authors such as Guberman et al. (1986) who define NCSE as a state lasting >60 min. Moreover, the EEG feature of high-voltage slow waves with an occasional spike component in patients with ring chromosome 20 is not found in the majority of NCSE patients either. Granner and Lee (1994), in analysing the EEG characteristics of NCSE, reported that atypical spike-and-wave complexes occurred as the predominant pattern in most cases, and rhythmic delta wave activity with intermixed spikes or sharp waves were found in 22 out of 78 patients. The clinical features of patients with ring chromosome 20 thus seem to constitute an atypical but distinct entity in the realm of NCSE, although a further comparative study of patients with and without ring chromosome 20 in a larger series is necessary to confirm this.

We propose that epilepsy associated with ring chromosome 20 constitutes a distinct syndrome characterized by NCSE with concomitant continuous bilateral high-voltage slow waves with occasional spikes, which usually lasts from several minutes to 1 h and occurs frequently, often daily. This epileptic state may accompany brief motor seizures or convulsive seizures presumably of focal origin. The seizures are resistant to antiepileptic medication.

Ring chromosome 20 and epilepsy

A ring chromosome is formed by the fusion of two arms of a chromosome. As is often the case with translocation, deletion of the distal parts of the chromosome can occur. The consequence of ring formation may, therefore, be loss of function normally associated with the deleted chromosome parts. Because deletion of the short arms (p11→pter) of chromosome 20 does not result in epilepsy (Kalousek and Therien, 1976), and terminal deletion of the long arm (q13→qter) is associated with epilepsy (Fraisse et al., 1981), some gene loss from the terminal segment q13.3→qter could be responsible for the manifestation of epilepsy (Thomsen et al., 1989). On the other hand, loss of genes from a chromosome may result in a disordered equilibrium of the residual genes, which could also play a role in the occurrence of epileptic seizures.

The locus of fusion in ring chromosome 20 was p13q3, p13q13.3 or p13q13.33 in all cases mentioned. The locus q13 is important for epilepsy, because two epileptic syndromes have been ascribed to the gene located in the neighbourhood. Autosomal dominant nocturnal frontal lobe epilepsy is a familial partial epilepsy causing frequent, violent, brief seizures at night, usually beginning in childhood (Scheffer et al., 1995). The gene for autosomal dominant nocturnal frontal lobe epilepsy was mapped to chromosome 20q13.2-q13.3 in one large Australian kindred (Phillips et al., 1995). Moreover, the neuronal nicotinic acetylcholine receptor alpha 4 subunit (CHRNA4) was mapped to the same region of 20q (Steinlein et al., 1994), and the gene is expressed in all layers of the frontal cortex. Mutations in the CHRNA4 gene is implicated in autosomal dominant nocturnal frontal lobe epilepsy (Steinlein et al., 1995). Benign familial neonatal convulsions is a rare autosomal dominant disorder characterized by uncomplicated seizures in the first few weeks of life (Hirsch et al., 1993). One locus for this condition was mapped to 20q1.2–1.3 (EBN1), which is very close to the autosomal dominant nocturnal frontal lobe epilepsy gene (Leppert et al., 1989), and Beck et al. (1994) demonstrated a nonsense mutation in the CHRNA4 gene that cosegregated with the 20q-linked form of benign familial neonatal convulsions. An investigation as to whether there is a rearrangement in the CHRNA4 gene in patients with ring chromosome 20 may help in understanding their epilepsy.

Most of the epilepsy in patients with ring chromosome 20 showed an EEG expression of prolonged high-voltage slow waves. It was suggested that the gene responsible for a normal low-voltage variant of the human EEG mapped to the distal part of chromosome 20q (Steinlein et al., 1992). The main characteristic of the low-voltage variant of the human EEG is the absence of rhythmic alpha activity, especially in occipital leads, whereas other wave forms such as beta or theta waves may be present (Anokhin et al., 1992). The phenotypes ‘repression of alpha waves’ in the low-voltage variant of the human EEG and ‘induction of high voltage paroxysms’ in epilepsy-ring chromosome 20 syndrome stand in clear contrast to each other. One may assume a centre such as one for the regulation of neuronal synchronicity in the neighbouring genes that may be responsible for both phenotypes. Genetic investigation of patients with epilepsy and ring chromosome 20 may add important evidence of brain dysfunction that contributes to the clarification of the epileptogenic mechanism.

Lastly, a few words relating to mosaicism. Mental retardation was not prominent in our patients and there were no patients with distinct dysmorphism. The percentage of r(20) loading cells among the lymphocytes was not increased in our patients. The patients reported in the literature having no or slight dysmorphic features also had a low rate of r(20) mosaicism. The severity of dysmorphism or intellectual dysfunction may correlate with the increasing ratio of the abnormal cells, although the severity or refractoriness of the epileptic seizures does not seem to relate to the degree of mosaicism.
References


