Case report

Mosaicism and phenotype in ring chromosome 20 syndrome


Ring chromosome 20 [r(20)] syndrome is a rare chromosomal disorder characterized by epilepsy, mild to moderate mental impairment, and malformation. Patients generally show mosaicism in 1–100% of lymphocytes with r(20). We report here a patient with r(20) syndrome who exhibited mild phenotype with the small ratio of mosaicism (13%) with r(20). Although previous small-scale studies concluded that the mosaicism ratio was unrelated to clinical phenotype, our reassessment of all 57 reported cases has revealed that the ratio is significantly associated with age at seizure onset, intelligence quotient, and malformation, but not with the response of epilepsy to drug treatment. Our results provide important clinical information and prediction for r(20) syndrome.

A ring chromosome is a chromosomal aberration and is formed by fusion of the deleted ends of both chromosome arms (1). Ring chromosome 20 [r(20)] syndrome is a rare disease characterized by epilepsy, mild to moderate mental impairment, and malformations that include cardiovascular anomalies, facial dysmorphism, and microcephaly (2–4). Patients generally show mosaicism in 1–100% of lymphocytes with r(20). Although only 57 patients have been reported previously (5–9), this disease is electroclinically important because it is associated with non-convulsive status epilepticus (6, 10–12). Recent studies report that non-convulsive status epilepticus is more common than generally appreciated and is found in various diseases with abnormal mental status and memory dysfunction, similar to symptoms in demented patients (13). Therefore, a better understanding of r(20) syndrome may help to clarify the genetic factors underlying non-convulsive status epilepticus. In this report, we describe a patient with r(20) syndrome who had adolescent-onset epilepsy, mild mental impairment, and no malformation. Thirteen percent of lymphocytes had r(20). We hypothesized that her mild phenotype is because of the small ratio of mosaicism with r(20). However, previous studies concluded that the ratio of mosaicism was unrelated to intelligence quotient (IQ) and age at seizure onset (7, 14). Because this conclusion was based on a limited number of patients and non-uniform evaluation criteria, we reassessed all reported cases of r(20) syndrome to establish a clearer definition of this disease and to examine the relation between the mosaicism ratio and clinical phenotype.

Case report

A 36-year-old woman had no family history of epilepsy or major anomalies. After an uncomplicated birth, the patient’s early development was normal, except for two episodes of febrile convulsions. At 17 years of age, absence seizures lasting for approximately 10 s developed and recurred more than 10 times per day. She started to have progressive mental impairment. The frequency of seizures was reduced by various antiepileptic medications, including phenobarbital, carbamazepine, and phenytoin, but she still had absence and generalized tonic seizures once a month. At 36 years of age, a chromosome analysis revealed that 13% of lymphocytes had r(20), 3% had monosomy 20, and 84% had normal chromosomes. The r(20) had breakpoints at p13 and...
q13.33. The patient’s electroencephalogram (EEG) showed diffuse high-voltage theta waves (4–5 Hz; 100–150 µV) and occasional spike and wave complexes over the front-polar area during her awake state, consistent with the findings of non-convulsive status epilepticus in r(20) syndrome (6). The results of computed tomographic, magnetic resonance imaging, and single-photon emission computed tomographic examinations were normal.

Statistical analyses

We summarized the clinical information obtained from our patient and from 57 patients with r(20) syndrome (24 males and 34 females) and nine with supernumerary r(20) syndrome (seven males and two females) who were described in the literature. The ratio of mosaicism, age at the onset of seizures, and IQ were analyzed by linear regression analysis. The ratio and incidence of malformations or drug responsiveness were analyzed with Student’s t-test. All statistical analyses were performed with STATVIEW software.

Table 1 Clinical characteristics of r(20) syndrome and supernumerary r(20) syndrome

<table>
<thead>
<tr>
<th></th>
<th>r(20) syndrome</th>
<th>Supernumerary r(20)</th>
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<tbody>
<tr>
<td>Karyotype</td>
<td>46, r(20)</td>
<td>47, +r(20)/48, +2r(20)</td>
</tr>
<tr>
<td>Age</td>
<td>6.07*</td>
<td>2.92†</td>
</tr>
<tr>
<td>Sex</td>
<td>M: 24, F: 34</td>
<td>M: 7, F: 2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>97% (56/58)</td>
<td>0% (0/9)</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>77% (40/52)</td>
<td>67% (6/9)</td>
</tr>
<tr>
<td>Anomaly</td>
<td>39% (17/44) (mild: 15, severe: 2)</td>
<td>100% (9/9) (multiple)</td>
</tr>
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</table>

* Age at seizure onset.
† Age at clinical examination.

Results

The clinical characteristics of r(20) and supernumerary r(20) syndromes are shown in the Table 1. Age at the onset of seizures ranged from 4 months to 21 years (mean age: 6.07 ± 4.84 years). The ratio of r(20) ranged from 1 to 100 (mean ratio: 54.7 ± 34.50%). IQ ranged from 33 to 103 (mean IQ: 67.2 ± 20.31). Mental impairment was present in 40 of 52 (77%) subjects. The ratio of r(20) inversely correlated with age at seizure onset and with IQ (Fig. 1A and B). Major malformations (4.5%), including cardiovascular anomalies, and minor malformations, including facial dysmorphism (27%) and microcephaly (22%), were more frequent in patients with high mosaicism ratios (Fig. 1C). There were only two reports in which seizures completely responded to medical therapy (15, 16), but others noted a partial response (11 patients) or refractoriness (11 patients) to medication. Drug responsiveness did not correlate with the ratio of r(20), because the mean ratio (SD) for the complete or partial drug responsiveness was 60% (35) and that for the medical refractoriness was 53% (30), P = 0.6.

Discussion

Clinical symptoms of r(20) syndrome may be caused by a partial monosomy since a ring chromosome is thought to arise from deletions of telomeric regions (17). On the other hand, r(20) is sometimes identified as an extra chromosome besides two normal ones and hence gives rise to the clinical picture of a partial trisomy (18). This supernumerary r(20) causes multiple anomalies but
no epilepsy, and the resulting syndrome should be differentiated from r(20) syndrome (Table 1). In the literature, however, these two syndromes have been often confused (14). We therefore define r(20) syndrome as a disease in which the majority of lymphocytes with abnormal karyotype have one normal chromosome with the other replaced by a ring chromosome.

Exclusion of patients with supernumerary r(20) and statistical analysis of all reported cases of r(20) syndrome showed that IQ and age at seizure onset inversely correlated with the ratio of mosaicism. We also found that malformations were associated with higher ratios of mosaicism. The low mosaicism ratio in our patient may thus account for the mild phenotype.

The EEG in r(20) syndrome is characterized by concomitant continuous bilateral high-voltage slow waves with occasional spikes. This EEG activity is associated with non-convulsive status epilepticus causing symptoms similar to those associated with dementia (6, 10–12). Seizures often do not respond to antiepileptic medication (3, 14, 19). Our patient had non-convulsive status epilepticus and absence and generalized tonic seizures that partially responded to multiple antiepileptic drugs. The relatively mild signs and symptoms of epilepsy may have resulted from the low ratio of mosaicism. However, our statistical analysis showed no association of the mosaicism ratio with drug responsiveness, suggesting that other factors, such as the site of the deleted portion of r(20), may affect treatment response.

The mechanism underlying epilepsy in r(20) syndrome remains unknown. Two possibilities have been raised previously: (1) a structural abnormality of a ring chromosome that delays cell proliferation during development of the brain, and (2) deletions of certain telomeric genes. The first possibility seems unlikely because supernumerary r(20) syndrome does not show epilepsy. The second possibility is partly supported by the fact that terminal deletion of 20q causes epilepsy (20). The breakpoint of r(20) in our patient was 20q13.33, similar to most patients. This telomeric region includes two genes related to autosomal dominant epilepsy: niconitic acetylcholine receptor alpha-4 subunit (21) and potassium voltage-gated channel subfamily KQT member 2 (22). This finding suggests the hypothesis that the subjacent deletion in r(20) affects these genes, leading to an epileptic channelopathy (6). This hypothesis is plausible because a similar association between a ring chromosome and an autosomal-dominant disease has been reported for ring 17 chromosome and Miller–Dieker syndrome (23).

We conclude that the mosaicism ratio is significantly associated with age at seizure onset, IQ, and malformation, but not with the response of epilepsy to drug treatment in patients with r(20) syndrome, providing important clinical information and prediction for this disease. However, the ranges in age at onset and IQ for a given ratio are relatively wide, and therefore, the prediction of phenotype from the ratio should be cautious, particularly regarding genetic counseling. Further investigation of this disease may clarify the mechanism of epilepsy, especially that responsible for non-convulsive status epilepticus.

References

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