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Gelastic seizures in ring chromosome 20 syndrome: a case report with video illustration

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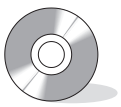
ABSTRACT – Although increasingly recognised, ring chromosome 20 (r[20]) syndrome is still diagnosed with delay, sometimes leading to inappropriate presurgical evaluation. The focal, presumed frontal, character of the seizures manifesting with fear and hypermotor behaviour and episodes of non-convulsive status epilepticus (NCSE) are most typical, as well as cognitive impairment with behavioural problems and, sometimes, dysmorphic signs. We present a girl diagnosed at the age of 13 years who suffered from an atypical clinical presentation, with minimal cognitive problems, absence of dysmorphic symptoms, and hypermotor/gelastic seizures. [*Published with video sequences*]

Key words: frontal, gelastic, ring 20 syndrome, non-convulsive status epilepticus, hypermotor



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Ring chromosome 20 (r[20]) syndrome is one of the chromosomal abnormalities almost always associated with epilepsy (Ville *et al*., 2006). Intellectual and behavioural disabilities of variable degree are important comorbidities, yet no particular dysmorphism is present. An early diagnosis is usually difficult, since the condition tends to worsen over time, although specific electroclinical patterns have been found to be very helpful in many cases (Canevini *et al*., 1998). The epilepsy phenotype has a particular age-related expression with non-specific seizure features in the neonatal period and early childhood, and only thereafter, frequent focal seizures with ictal terror, hallucinations, automatisms and hypermotor signs, as well as the appearance of episodes of non-convulsive status epilepticus (NCSE) with prolonged confusion (Inoue *et al*., 1997; Ville *et al*., 2006; Vignoli *et al*., 2009).

The EEG features in this second and more characteristic period consist of the following:

1) a (nearly) normal EEG activity with inconstant runs of slow waves in fronto-central areas without physiological reactivity;

and 2) long-lasting high-voltage slow waves with occasional spikes of frontal predominance (Inoue *et al*., 1997; Canevini *et al*., 1998; Kobayashi *et al*., 1998; Augustijn *et al*., 2001).

Major cognitive and behavioural disturbances have been clearly associated with a high incidence of pharmacoresistant seizures (Augustijn *et al*., 2001; Ville *et al*., 2006; Vignoli *et al*., 2009) and recently a genotype-phenotype correlation was confirmed by molecular analysis (Conlin *et al*., 2011). According to this and previous studies, non-mosaic patients have early epilepsy and more extensive comorbidities, whereas mosaicism is related to a later seizure onset and a lower likelihood of additional intellectual disability and dysmorphic features (Nishiwaki *et al*., 2005; Herrgard *et al*., 2007; Conlin *et al*., 2011). Although r(20) can be simply diagnosed by cytogenetic analysis of sufficient cells (*i.e*. 100 mitoses) to identify mosaicism, usually there is a considerable time lag from disease onset to diagnosis. Many uninformative clinical, including in some cases presurgical, investigations are undertaken due to AED failure and progressive neuropsychological impairment. The electroclinical picture suggesting focal, most often frontal, epilepsy may wrongly guide the diagnostic work-up. Usually, frequent tonic and hypermotor seizures with intense terror and multiple "subtle" nocturnal episodes are found to correspond to focal and/or lateralising features of the EEG (Inoue *et al*., 1997; Canevini *et al*., 1998; Kobayashi *et al*., 1998; Augustijn *et al*., 2001).

We report a r(20) case, diagnosed four years after the onset of drug-resistant epilepsy. The most typical seizures were hypermotor with a prominent gelastic phase correlating to interictal and ictal EEG findings of frontal, sometimes with right predominance, rhythmic slow-wave and epileptiform activity. Because of the refractoriness of the seizures, the need for presurgical evaluation was discussed. The overall appearance of the EEG, however, was strongly suggestive of r(20) and cytogenetic testing was performed, proving r(20) mosaicism.

Case study

A 13-year-old girl was the first and only child of healthy, non-consanguineous parents, without family history of neurological disorders. No significant problems during pregnancy and delivery were reported. The psychomotor development was normal and the child attended regular school. Since the age of nine, seizures with staring appeared, followed by laughter, jumping, arm waving, shouting, and sometimes urination at the end. They lasted up to 3-4 minutes; were multiple, and occurred mostly towards the evening. During the night and predominantly while falling asleep, brief episodes of strange, chaotic and very marked limb movements, usually accompanied by laughing, were reported to occur in series. Postictal confusion and speech disturbance were never noticed. After a nocturnal generalised tonic-clonic seizure one month after the disease onset, brain CT was performed and revealed no pathology. EEG showed normal background and bilaterally synchronous epileptiform activity with left-sided fronto-temporal predominance. Treatment with low-dose carbamazepine (CBZ) and subsequent oxcarbazepine (OXC) had no beneficial effect. Clonazepam (CZP) led to some seizure reduction with a longest seizure-free interval of two days. In the next EEG, a right-sided fronto-temporal focus was described. Brain MRI revealed no abnormalities. During the next two years, the seizures persisted at a frequency of one to several per day, without change in their characteristics. Learning problems mainly in the form of inattention occurred.

During the first admission to the Child Neurology Clinic in Sofia at the age of 11, EEG was interpreted as showing generalised paroxysmal activity. OXC was replaced by valproate (VPA) and levetiracetam (LEV), both added to CZP at an unchanged dose. The seizures increased to more than 30 a day and the child was referred again to the clinic. No physical or neurological abnormalities were found. The video-EEG demonstrated almost continuous bifrontal slow-wave and epileptiform activity, and ictal episodes every 30 seconds to 5 minutes, with altered consciousness, laughter, agitation, and hyperkinetic automatisms (*see video sequence*). The seizures lasted up to three minutes and were not followed by postictal deficit including language problems. The child did not recall the events and never reported any aura, or any specific and pleasant sensation, including mirth. The ictal EEG changes were multiphasic and corresponded to the clinically distinct transition from motionless state with stare to smile and subsequent laughter with hypermotor automatisms, with fast postictal orientation and reactivity without deficits at the end of the seizure (*figure 1*). Intravenous administration of diazepam did not change the frequency or characteristics of the ictal EEG episodes, but led to more subtle expression (only in the form of a smile) during the drug-induced sleep. LEV was switched to CBZ, and the gelastic hypermotor seizures gradually disappeared. No more nocturnal episodes were reported, but school problems persisted and even increased. The next MRI of higher resolution was again normal.

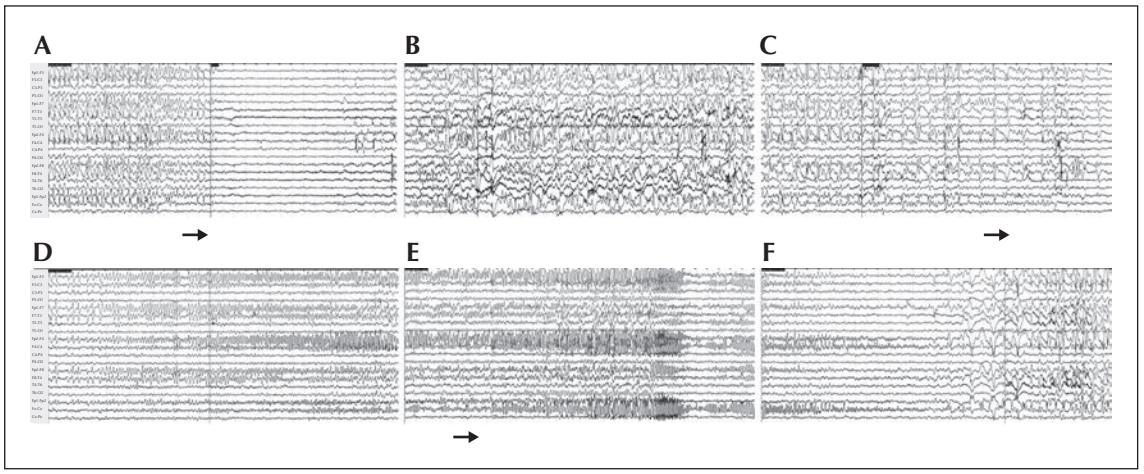

Figure 1. Interictal and ictal EEG presented as epochs of 30 seconds at a sensitivity of 10 μV/mm.
A) Interictal trace of bifrontal slow waves with increasing frequency. B) The first ictal change (arrow) is the progressive build-up of rhythmic sharp theta activity in the same regions with higher amplitude on the right, corresponding to staring, looking around, and a motionless state of the child for about 30 seconds (clinical onset marked by vertical line). C) After some waning of this rhythm and persistence of faster lower-amplitude activity on the right frontal region, higher-amplitude and slower epileptiform discharges appeared in both frontal regions and coincided with a smile (marked by arrow). D) Progressive frequency increase of the fronto-temporal slow SW activity is seen for about 30 seconds. Forced laughter then manifests, correlating to a sudden attenuation of the EEG activity with persistent right frontal, fast, low-voltage activity (vertical mark). E) During the subsequent hypermotor phase, about 20 seconds later (onset marked by arrow), slow waves and high-amplitude, irregular and slow SWs are seen with clear frontal predominance. F) The end of the clinical and electrographic seizure is inconspicuous with a gradual change to interictal state.

At two subsequent visits during the next year, the child appeared to react and speak slower, yet the neurological examination and AED serum levels were normal. The video-EEG demonstrated very frequent episodes (every 30 seconds to 3 minutes) of rhythmic, frontal slow-wave and epileptiform activity, during which the patient was not responding for up to three minutes (*figure 2*). Psychological testing revealed intellectual functioning at the lower age range with IQ of 88 (verbal IQ=85, non-verbal IQ=94). Significant attention deficit, impaired long-term memory, and delayed task performance were found. The psychological profile was of introverted personality with distant manner, social avoidance, and occasional aggressive bursts.

Although an alternative treatment and the potential need for extensive presurgical examinations were discussed with the parents on previous occasions, the uniform electroclinical picture, corresponding in general to NCSE, led us to suspect the diagnosis of r(20). Cytogenetic testing on 50 mitoses in two independent lymphocyte cultures revealed a mosaic female karyotype 46,XX,r(20)[12]/46,XX[38], indicating that 25% (*n*=12) of the cells carried ring 20 chromosomes. Later, lamotrigine as add-on treatment instead of VPA did not improve the condition of the patient, and topiramate at low doses reduced the frequency of the absence-like seizures. Thus, up to now, no AED treatment led to seizure control.

Discussion

This is the first Bulgarian patient with cytogenetically confirmed r(20), demonstrating the typical delay of diagnosis of the syndrome. We believe this case provides useful insight since, on one hand, the patient was diagnosed on the basis of the very informative and characteristic electroclinical picture of NCSE, and on the other hand, the patient initially presented with gelastic seizures. To the best of our knowledge, this is the first description of this rare seizure type in r(20). The approximately 100 cases published so far (Conlin *et al*., 2011) have shown manifestation of focal seizures consisting of ictal terror with frightened expression, loss of consciousness, oroalimentary automatisms and/or unspecified automatic behaviour, and hypertonia, correlating to frontal-onset discharge or ictal EEG changes suggestive of fronto-temporal seizure origin (Inoue *et al*., 1997; Canevini *et al*., 1998; Augustijn *et al*., 2001; Ville *et al*., 2006; Vignoli *et al*., 2009). For almost three years, our patient suffered stereotyped seizures of multiphasic character. The initial hypomotor and unresponsive state correlated to bifrontal slow-wave activity, which evolved to faster bifrontal theta rhythm. A trace attenuation and subsequent high-voltage, slow, spike-and-wave (SW) activity with the same distribution corresponded to the ictal laughter and the hyperkinetic phase, respectively. As shown in the figure in these very frequent seizures, not

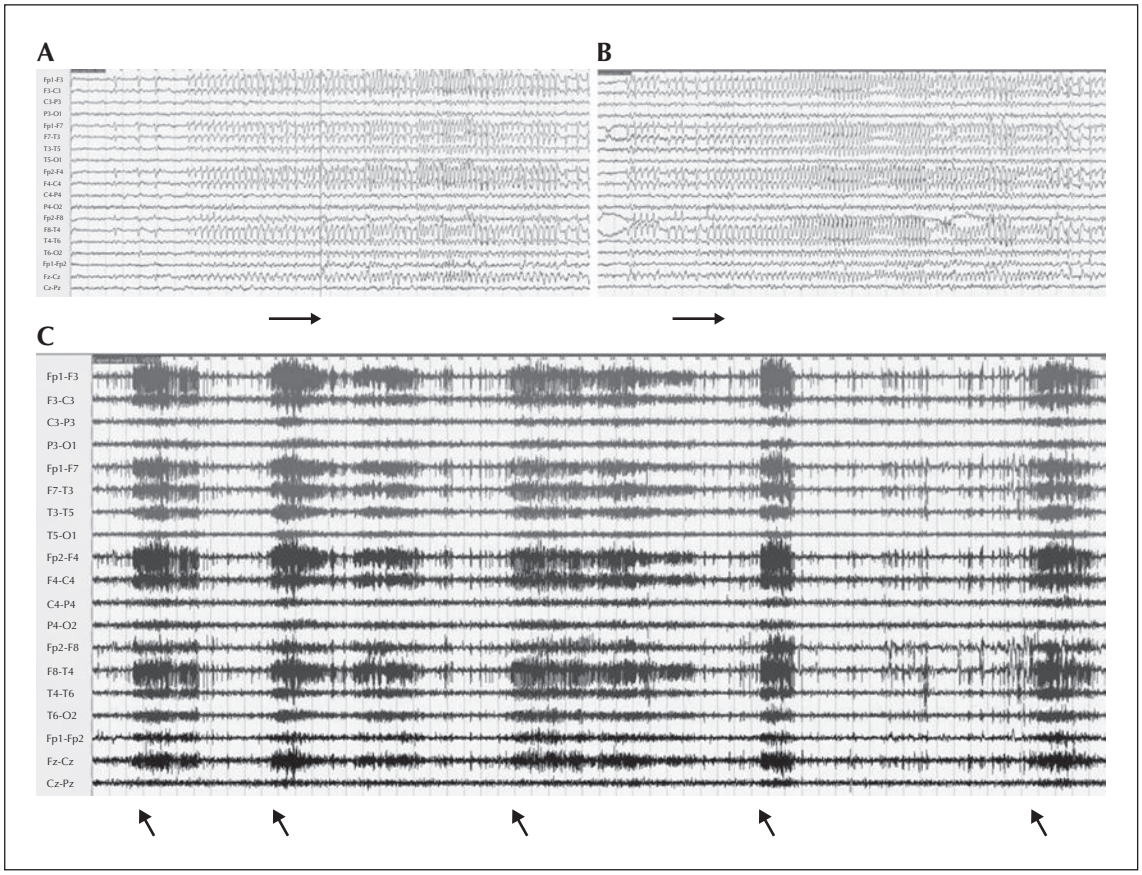

Figure 2. A and B) Ictal EEG of two subsequent "absence-like" seizures. The child is staring and not responding (clinical onset is marked by an arrow). The changes in the trace are generally the same as in the first two phases of gelastic hypermotor seizures, recorded eight months earlier. C) During the presented period of 10 minutes, five such seizures of variable duration can be differentiated (marked by arrows).

substantially aborted by intravenous diazepam application, the ictal discharge was clearly starting and maximal over the frontal regions with slight right-side predominance. We believe this case adds further support to the hypothesis of focal seizure origin in r(20), corroborated by most of the observations, with few exceptions (Ville *et al*., 2006). The interictal and ictal EEG changes remained maximal over the frontal regions, also during the NCSE period, highlighting the crucial role of the frontal lobes in the epileptogenesis of this disorder and giving us reason to suspect r(20).

Gelastic seizures have been classically associated with hypothalamic hamartomas, although other aetiologies and extra-hypothalamic locations have been described. Most often, gelastic seizures, lesional or not, were demonstrated to originate from epileptogenic areas in the frontal lobes, by means of various techniques (Sartori *et al*., 1999; Cheung *et al*., 2007; Umeoka *et al*., 2008; Unnwongse *et al*., 2010) and especially in the mesial premotor cortex (McConachie and King, 1997; Chassagnon *et al*., 2003; Mohamed *et al*., 2007), as well as in the (mesio)-temporo-basal structures (Iwasa *et al*., 2002; Dericioglu *et al*., 2005; Oehl *et al*., 2009). The clinical features of gelastic seizures related to frontal or temporal *foci* differ in terms of the presence of a subjective emotional component. The feeling of mirth has been associated with seizures from the temporal lobe, while lack of mirth or pleasant sensations are characteristic of seizures of frontal origin (Cheung *et al*., 2007). A dipole source localisation study of gelastic seizures, with or without sense of mirth, confirmed the generation of these two types of seizures in different structures, *i.e*. the hippocampal region and the anterior cingulate region (Iwasa *et al*., 2002). Also, motor symptoms are usually present or more prominent in frontal lobe gelastic seizures, in contrast to those originating in the temporal lobe, although atypical cases are reported as well (McConachie and King, 1997; Cheung *et al*., 2007). Our patient's gelastic seizures had the typical appearance of frontal gelastic seizures, since mirth was never recalled and reported by the patient, but the seizures

had prominent motor (hyperkinetic) manifestations. Therefore, we believe our case points again to the leading role of the frontal lobes in r(20) epilepsy, which was also confirmed by an ictal magneto-encephalographic study in one case (Tanaka *et al*., 2004).

Comparing the semiology of our patient's gelastic seizures with that of gelastic seizures in hypothalamic hamartoma (Oehl *et al*., 2010), we found some differences. In our patient, and in contrast to children with hypothalamic hamartoma, the gelastic component of the seizures was very marked, yet not the initial and dominating semiological element, since it was always preceded by a hypomotor phase and followed by hypermotor behaviour, both lasting for more than 20-30 seconds. Accordingly, the seizures in our case were significantly longer (approximately 2 minutes) than those in children with hypothalamic hamartoma (mean total seizure duration: 15.6 seconds; mean duration of the gelastic component: 11.6 seconds). In the study of Oehl *et al*., staring and behavioural arrest at seizure onset were relatively rare in children (together, they were found in only 8% of seizures and each was present in 20% of the patients), in contrast to our patient's seizures where these signs were always the initial seizure events. On the other hand, hypermotor behaviour was never observed during the seizures in children with hypothalamic hamartoma, but was always present and very prominent during the seizures of our patient.

In the above-mentioned study (Oehl *et al*., 2010), during the individual course of epilepsy in hypothalamic hamartoma, the seizure semiology could change such that seizure onset occurred with non-gelastic components and seizure duration tended to be prolonged with age and epilepsy duration. In our case, a modification of the seizure semiology (from gelastic-hypermotor to complex partial seizures of dialeptic type) was only seen on change of the anticonvulsant medication and the seizure duration, in general, remained long (from about 25 to more than 120 seconds; *figure 2*). As we found no previously published r(20) cases with gelastic seizures, we cannot claim that this is the usual development of epilepsy with gelastic seizures in r(20) syndrome.

Our patient showed no dysmorphic features that could suggest a chromosomal disease and cognitive functioning was not substantially reduced, even during the course of frequent and refractory seizures with constant EEG abnormalities. Most probably, the increasing learning problems during the second period were related to the multiple seizures of dialeptic type, having greatest impact on attention and concentration. We assume that the relatively low level of mosaicism (25%) in our patient determined the later seizure onset and minimal intellectual dysfunction, in spite of the typical electroclinical picture, similar to other reported cases (Nishiwaki *et al*., 2005). Therefore, we believe this clinical presentation to be another example of the typical genotype-phenotype correlation in r(20), which was recently confirmed (Conlin *et al*., 2011). This molecular genetic study has clearly shown that the overall predominating mosaicism in r(20) (about two thirds of the reported cases so far) is related to an older age at epilepsy onset (mean: 6 years) and a lower incidence of dysmorphic and neuropsychological abnormalities (Conlin *et al*., 2011). Mosaic and non-mosaic rings are formed by different mechanisms, making r(20) a genetically heterogeneous disorder which determines the phenotypic spectrum. We believe our case of frontal gelastic seizures expands the phenotypic variability of epilepsy in r(20). Although the challenge with regards to elucidation of pathophysiology and therapeutic modification remains, this disorder can be diagnosed easily, earlier, and more frequently; the clue being the characteristic EEG (Kobayashi *et al*., 1998), which was confirmed in our case. □

Legend for videosequence

The video-EEG sequence shows a gelastic hypermotor seizure of the patient. Symptoms appeared in the following order: motionless staring and looking around, smiling, laughing, agitation with persistent laughter, and hyperkinetic behaviour. The seizure ends with a gradual recovery without postictal language and motor deficit. Ictal EEG changes are multiphasic with clear frontal predominance, the onset of laughter being related to a trace attenuation and right-sided, predominantly frontal, low-amplitude, fast activity.

Key words for video research on www.epilepticdisorders.com
Syndrome: epilepsy not classified
Etiology: ring chromosome 20
Phenomenology: gelastic seizure; hypermotor seizure
Localization: not applicable

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