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Partial epilepsy complicated by convulsive and nonconvulsive episodes of status epilepticus in a patient with ring chromosome 14 syndrome

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ABSTRACT – Epilepsy is the most common and serious neurological symptom in ring chromosome 14 syndrome, also characterised by mild dysmorphisms, acquired microcephaly, cognitive impairment, hypotonia and ocular abnormalities. Typically, early-onset, polymorphous and drug-resistant seizures are reported. Status epilepticus has not been previously reported. We describe a nine-year-old Caucasian boy with ring 14 syndrome who presented a severe early-onset and drug-resistant focal epilepsy with secondary generalised seizures and repetitive episodes of convulsive and non-convulsive status epilepticus. The electro-clinical evaluation of prolonged seizures and their long-term consequences is important for the practical management of these patients and for a better comprehension of the syndrome.

Key words: ring 14 chromosome, epilepsy, status epilepticus, nonconvulsive status epilepticus

Epilepsy is one of the most relevant central nervous system manifestations in ring 14 chromosome syndrome. It is a rare cytogenetic disorder, reported so far in about 50 patients, caused by the fusion of two broken chromosome ends which form a ring chromosome, usually associated with loss of a small amount of genetic material. A recognisable phenotype consisting of psychomotor delay, cognitive disability, hypotonia, feeding and growth difficulties, microcephaly, ocular retinal abnormalities and seizures is based on an accurate clinical and genetic characterisation that emerged from a series of 20 patients included in the Ring 14 Association Database (http://www.ring14.org) (Zollino *et al.*, 2009). Dysmorphic features are usually mild and include a high and prominent forehead, an elongated face with puffy cheeks, widely spaced eyes with blepharophimosis and epicanthus, a flat nasal bridge with a prominent nasal tip and low-set ears (Zollino *et al.*, 2009; Van Karnebeek *et al.*, 2002).

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For all ring 14 patients examined, Zollino *et al.* (2009) described an early-onset epilepsy with polymorphous generalised and localisation-related seizures and frequent status epilepticus (SE), confirming earlier findings by Zelante *et al.* (1991). Only few case reports have focused on the electro-clinical features of the epilepsy which assessed associated severity (Ville *et al.*, 2009; Morimoto *et al.*, 2003). Moreover, data on the incidence of SE complicating this rare, so far poorly understood, syndrome are lacking. SE in the paediatric age group can present challenges for diagnosis and management because of the age-dependent vulnerability of patients and genetic predisposition. Moreover, non-convulsive status epilepticus (NCSE) poses further diagnostic and therapeutic problems, sometimes mimicking non-epileptic behavioural disturbances. For chromosomal disorders, a prompt identification of NCSE becomes more complex because of the underlying cognitive disability and associated behavioural problems, consequently leading to a delay in diagnosis and treatment. In this study, we describe clinical and EEG features of epilepsy and SE in a boy with ring 14 syndrome.

Case report

This nine-year-old boy is the second child of healthy, non-consanguineous parents, born at term after an uneventful pregnancy and delivery. Family history included multiple abortions and mental retardation but not epilepsy. Neonatal weight was 3.25 kg (10^{th}-25^{th} centile). Apgar scores were nine and ten at one and five minutes, respectively. Height was 47 cm (< 3^{rd} centile), and head circumference 34 cm (50^{th} centile). At birth he presented poor sucking and feeding difficulties, and hypotonia. In the first year of life he developed growth retardation and progressive microcephaly.

His clinical history was also complicated by a severe gastro-oesophageal reflux with oesophagitis, frequent respiratory and urinary tract infections and atopic dermatitis. Immunological examinations showed an IgA and IgG deficiency. Psychomotor development was characterised by slight motor and severe language delay. At last neurological evaluation (8 years, 10 months) his gait was characterised by mild equilibrium impairment, tip-toe walking and he could pronounce only few words. He was a good-natured boy with hyperkinetic and sometimes aggressive behaviour. A combination of postnatal microcephaly and minor anomalies including a prominent forehead, flat nasal bridge, apparent hypertelorism, low-set ears, a high-arched palate, puffy cheeks, small hands and cafè au lait spots *(figure 1)* suggested the presence of a chromosomal abnormality.

Comprehensive metabolic screening and brain MRI were normal.

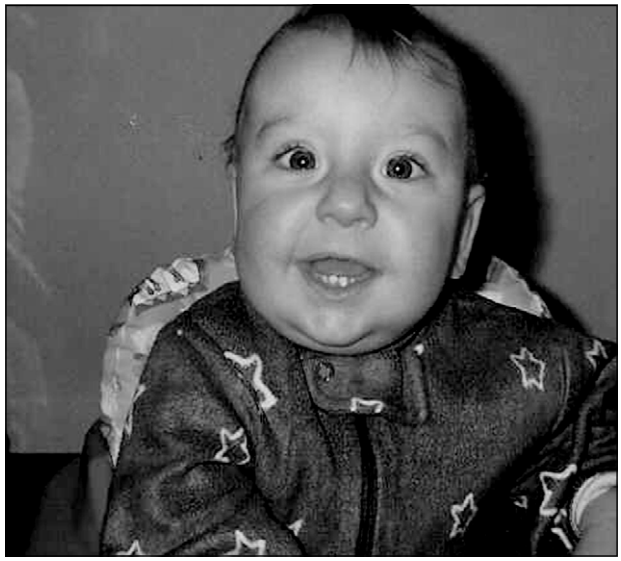

Figure 1. Patient at 14 months. Distinctive facial dysmorphisms: high and prominent forehead, elongated face with puffy cheeks, flat nasal bridge and apparent hypertelorism.

High resolution chromosome analysis showed a mosaic chromosome constitution 46, XY, r(14)del(14)(14q33.33) [80] / 45,XY, -14 [20]. A terminal 2.3 Mb 14q deletion was detected by FISH analysis, as previously reported (Zollino *et al.*, 2009).

At the age of 15 months he was admitted to the Child Neurology Unit because of the occurrence of long-lasting (four hours) afebrile repetitive seizures during sleep characterised by staring, loss of consciousness, breathing difficulties and generalised hypertonus, followed by four-limb clonias with a right mild predominance, resembling SE. The EEG recording during each seizure revealed bifrontal delta waves followed by an abrupt, three-second flattening of background activity after which rhythmic anterior triphasic slow waves with intermingled spikes appeared. This pattern was followed by left fronto-temporal fast rhythmic spikes with rapid diffusion to the right fronto-temporal regions. This activity rapidly generalised with prolonged irregular spike-waves, mostly 2-2.5 complexes/sec, and abruptly stopped after two minutes with a diffuse flattening, followed by the reappearance of background rhythms *(figure 2)*. Seizures were not responsive to intravenous diazepam and subsided completely only after intravenous lorazepam.

During the next three months, the patient had two more seizures, apparently described by parents as tonic-clonic generalised convulsions. Both seizures seemed to be facilitated by fever. Interictal EEG recorded some months later showed a well organised background activity with occasional synchronous and asynchronous spikes over the frontal regions during sleep *(figure 3)*.

Since the age of 18 months, he experienced clinical worsening with the occurrence of daily clusters of seizures,

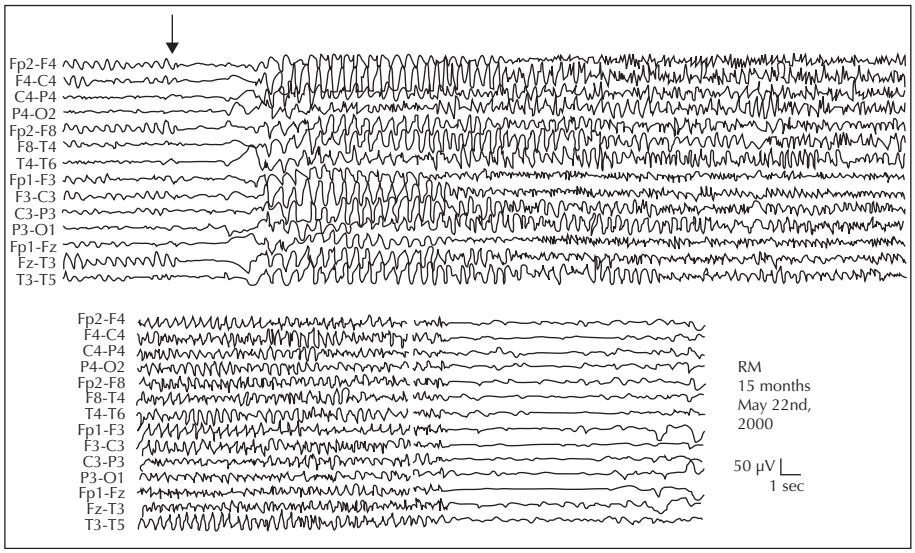

Figure 2. EEG performed at the age of 15 months: SE characterised by a series of frequently repeated seizures. Between seizures, delta waves predominated bilaterally in the frontal regions. Seizures started (arrow) with an abrupt, three-second long, attenuation of background activity followed by rhythmic anterior triphasic slow waves with intermingled spikes and subsequently by focal left fronto-temporal rhythmic spikes which rapidly reached the right fronto-temporal region. Ictal discharges rapidly became generalised with prolonged irregular 2-2.5 Hz spike-waves, and abruptly stopped after two minutes with a diffuse post-ictal flattening.

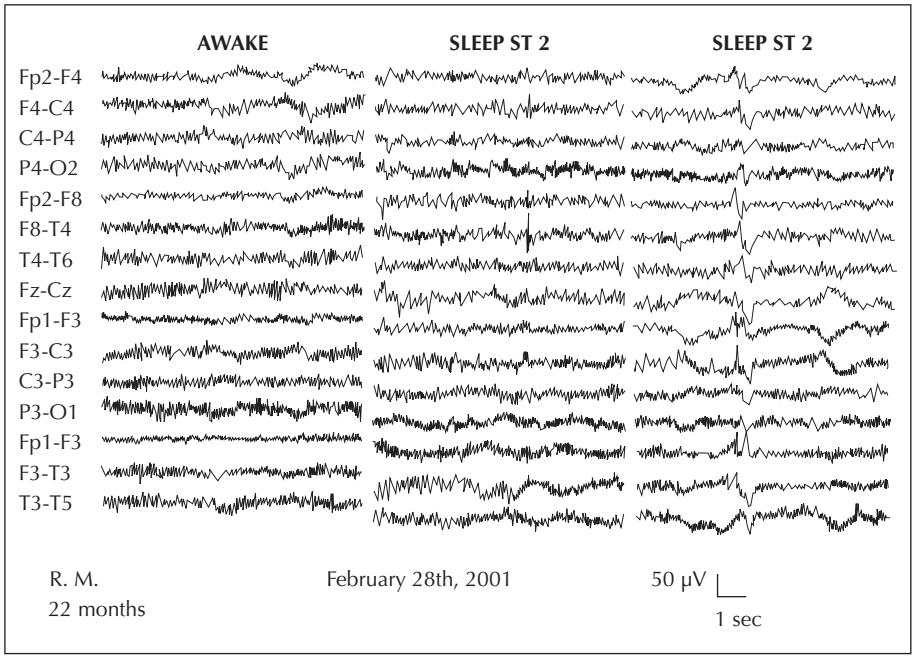

Figure 3. Interictal EEG recordings showed a well organised background activity with occasional asynchronous spikes over the frontal regions during sleep (in the middle and on the right).

mainly in drowsiness, characterised by staring, flushing, mydriasis, loss of consciousness, conjugate eye deviation to the right followed by upper arm dystonic posture and vibratory hypertonus. Convulsive seizures tended to last two to three minutes followed by prominent gestural and oro-buccal automatisms. In the following years, his epilepsy evolved into weekly and then monthly clusters of seizures, occurring in drowsiness or during sleep, with variable frequency and unmodified presentation. Seizures were usually long-lasting with a prolonged post-ictal phase but clearly did not resemble SE. His epilepsy became resistant to different combinations of several antiepileptic drugs.

Since the age of seven years, the patient presented a single (or very few) episode of repetitive convulsive seizures at home which were witnessed and occurred during morning sleep, characterised by staring, tonic eyes and head deviation, apnoea and vibratory hypertonus lasting up to five minutes. The seizures were usually followed by behavioural modification, mild confusion and a reduced motor repertoire. Due to the persistence of this state, the patient was admitted to the Neurology Unit and EEG monitoring showed a pattern of bilateral frontal high voltage continuous rhythmic delta activity occasionally intermingled with small epileptiform discharges *(figure 4)*. This pattern was occasionally replaced by brief periods of lower voltage background activity with theta frequency. Neurological examination during this state revealed an alert but non-responsive child and slow stereotyped movements that were not concordant with his usual hyperactive behaviour. Moreover, he seemed confused and hypotonic with alternating gestural automatisms and vegetative symptoms (flushing, mydriatic poorly reactive pupils). Treatment with 4 mg intravenous of lorazepam resulted in a poor EEG and clinical response. During infusion of intravenous phenytoin, continuous EEG recording documented a progressive reduction of the delta bilateral frontal activity. Clinically, the patient improved and two days later the EEG returned to the baseline with focal frontal interictal spikes *(figure 4)*. Despite polytherapy with phenytoin, oxcarbazepine, nitrazepam and pregabalin the patient tended to relapse on a monthly basis and revealed, in the acute phase, to be sensitive only to intravenous phenytoin.

Discussion

In this case study, we report a patient with ring chromosome 14 who had a documented clinical and EEG history of NCSE. Ring chromosome 14 is a rare cytogenetic disorder, with approximately 50 cases reported in the literature, described with a common phenotype. Most of the clinical features are also observed in 14q linear deletion patients, except for seizures and retinal abnormalities (Zollino *et al.*, 2009; Van Karnebeek *et al.*, 2002; Schlade-Bartusiak *et al.*, 2005). It therefore seems unlikely that a deletion at a specific locus should predispose patients to the overlapping clinical features associated with these two disorders. Alternative hypotheses have therefore been proposed to explain the prevalence of seizures in the ring 14 syndrome. These include: 1) somatic mosaicism that may vary in degree among different tissues and 2) position effect, leading to silencing of genes on the long arm of the chromosome juxtaposed to the short arm (Zollino *et al.*, 2009; Schlade-Bartusiak *et al.*, 2005).
The incidence of epilepsy in ring 14 syndrome is almost 100% and the reported seizures are frequently intractable and include different types. They may be generalised, partial or mixed with a variable but commonly early

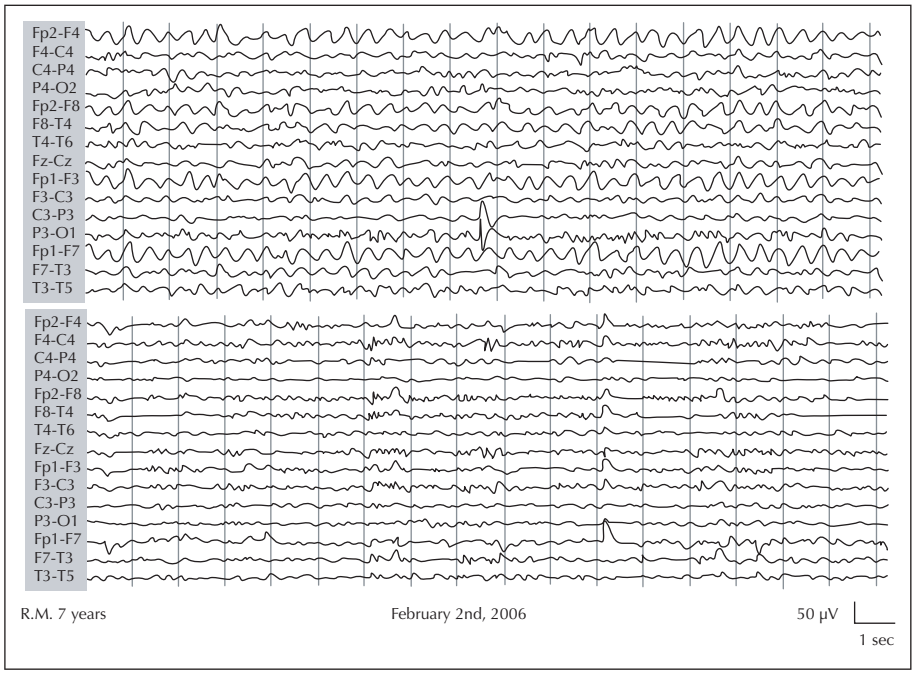

Figure 4. EEG recording showed bilateral frontal high voltage continuous delta activity (above) concomitant with a behaviour characterised by confusion, hypotonia, alternating gestural automatisms and vegetative symptoms. Continuous delta activity was resolved after intravenous bolus of phenytoin (below).

onset with recurring SE (Zollino *et al.*, 2009; Ville *et al.*, 2009; Zelante *et al.*, 1991). Some authors have reported observations of ring 14 chromosome presenting as an early-onset isolated partial epilepsy. In some cases, complex partial seizures were considered to be attributable to an underlying cerebral lesion (Shirasaka *et al.*, 1992; Ono *et al.*, 1999) but were also found in cases without a clearly detectable focal brain anomaly (Morimoto *et al.*, 2003). Except for these few case reports, a detailed clinical and EEG description of seizures and SE in large series of ring 14 syndrome is still lacking.

Here we describe a patient with a documented clinical and EEG history of focal epilepsy with secondary generalised seizures and recurrent SE. In our case, epileptic seizures at onset appeared to be difficult to classify as localization-related due to rapid secondary generalisation. Therefore, only the presence of focal abnormalities based on EEG and an accurate observation of seizure structure permitted the diagnosis of complex partial epilepsy, with seizures likely originating from left fronto-temporal regions. However, there was no evidence of focal brain abnormalities on MRI. This pattern is consistent with data reported by Morimoto *et al.* (2003) and Ville *et al.* (2009). A history of recurrent and unpredictable convulsive SE was one of the major concerning issues in this child's clinical course. Another intriguing feature of his epilepsy was the appearance of ideomotor slowing after a relatively short time following a convulsive episode. EEG recording of this clinical event consisted of long-lasting bifrontal rhythmic delta waves, with associated rare spikes, raising the question as to whether this pattern could represent an ictal activity, rather then a post-ictal event.

Even though continuous video-EEG recording seems to be the diagnostic tool for NCSE, it is often challenging to differentiate between an epileptiform activity and the expression of electric brain dysfunction when an uncommon EEG pattern is identified. A diagnosis of NCSE was suggested in our patient by the progressive fragmentation and subsequent resolution of an abnormal EEG pattern which was concomitant with an improvement of the behavioural state after intravenous phenytoin infusion. SE in the paediatric age group may pose challenges in diagnosis and management. SE may occur in patients with neurometabolic diseases, cortical malformations, chromosomal abnormalities and may be precipitated by abrupt discontinuation of antiepileptic drugs with short and long-term consequences on the immature and developing brain. In particular, in the context of partial epilepsy with frontal and temporal onset, NCSE poses many challenging nosologic, diagnostic and therapeutic problems due to a lack of clear clinical and electroencephalographic definition, and age-dependent genetic and other aetiological susceptibility factors, which lead to a delay in diagnosis and treatment. During a course of partial epilepsy with frontal and temporal onset, repetitive stereotyped non-convulsive seizures and/or altered mental or behavioural status may occur with little fluctuation and may mimic non-epileptic behavioural disturbances. Moreover, there are only few reports of NCSE correlated with persistent or continuous diffuse or focal (mainly frontal lobes) EEG rhythmic theta-delta activity with no or little intermingled epileptiform spikes (Kaplan, 2007; Treiman and Delgado-Escueta, 1983). We believe that this is the case for our patient.

Interestingly, such EEG patterns during NCSE are also a hallmark of ring 20 syndrome and the presence of NCSE is also a major diagnostic complication for other chromosomal abnormalities, of which one of the best-known is Angelman syndrome. The typical EEG pattern, recognised as "notch delta" can occur without any clear manifestation and children may experience prolonged periods of altered responsiveness with admixed myoclonias; it is still controversial whether myoclonic SE should be included as a form of NCSE (Pelc *et al.*, 2008). Myoclonic and atypical absences, sometimes lasting for days or even weeks, accompanied by impairment of consciousness, are also a frequent feature of Wolf-Hirschhorn syndrome (Kagitani-Shimono *et al.*, 2005). Among ring syndromes, the ring chromosome 20 syndrome is a recognisable clinical entity associated with mild mental deficiency, behavioural disorder and a specific phenotype consisting of complex partial seizures, nocturnal frontal lobe seizures and NCSE (Locharernkul *et al.*, 2005). Recently, a four-year-old boy with ring chromosome 17 and an early onset, drug-resistant epilepsy and prolonged diurnal SE, was reported with a clinical and EEG pattern similar to that of ring 20 patients (Ricard-Mousnier *et al.*, 2007). It is striking to note that the main aetiologies associated with NCSE in children are chromosomal abnormalities, especially ring chromosome syndromes. These findings suggest the possibility of a common specificity and pathogenesis of epilepsy in ring chromosome syndromes.

Finally, a high level of suspicion is certainly necessary to recognise NCSE since, although common, it is an underdiagnosed medical emergency. The most common presentation of NCSE is in the case of a supposedly controlled convulsive status epilepticus, but also after short isolated clinical seizures or between convulsive recurrent ictal events, as in our patient. Of particular concern is the fact that clinical symptoms may be indistinguishable from those of a post-ictal event or other non-epileptic disorders. Furthermore, in patients with chromosomal abnormalities the behavioural disturbance and cognitive impairment frequently observed makes it conceivably more difficult to establish a clear clinical distinction between basal state and NCSE. Since NCSE is a treatable entity, EEG examination should therefore be a routine part of evaluation in these children, as in the case of our patient, in which continuous EEG monitoring, performed after the appearance of isolated convulsive seizures, may identify

NCSE and aid the choice of treatment. To our knowledge, this is the first report of a comprehensive description of EEG features and clinical presentation of SE in a patient with ring 14 syndrome. Further cases are necessary to establish the incidence and characteristics of NCSE in children with this rare chromosomal abnormality. □

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Disclosure.
None of the authors has any conflict of interest to disclose.

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