

Ring 17 syndrome: first clinical report without intellectual disability

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Received January 28, 2014; Accepted November 17, 2014

ABSTRACT – Ring chromosomes are rare abnormalities caused by the fusion of the telomeric regions. Three-ring chromosome syndromes (Cr 20, Cr 17 and Cr 14) cause epilepsy with variable phenotypes. In ring 17 patients with mild phenotype, some authors have shown an epilepsy syndrome similar to that of ring 20. We report the first case of a girl with ring chromosome 17 and a normal neurological and general cognitive profile. She had had, from 9 years old, focal pharmacoresistant epilepsy associated with episodes of non-convulsive status epilepticus with mainly autonomic features. Cytogenetic analysis revealed an abnormal karyotype characterised by the presence of *de novo* ring chromosome 17 in 19% of metaphases. The array CGH (100 KB) did not show any genetic deletion. The clinical and epilepsy phenotype was, to a certain degree, similar to that of ring 20 syndrome.

Key words: ring 17 syndrome, ring 20 syndrome, focal epilepsy, chromosome analysis

Ring chromosome abnormalities can affect all the chromosomes and are caused by the fusion of telomeric regions. Three-ring chromosome syndromes (Cr 20, Cr 17 and Cr 14) cause epilepsy with variable phenotypes; the severity of the phenotype in each syndrome is correlated with the extent of chromosome deletion and the degree of somatic mosaicism (Kosztolanyi, 1987; Teyssier *et al.*, 1992; Surace *et al.*, 2009).

In ring chromosome 17 syndrome, the clinical phenotype is influenced by the deletion of the critical region for Miller Dicker syndrome (17p13). In patients with this deletion, the phenotype is characterised by lissencephaly, severe intellectual disability, and multifocal epilepsy. A mild phenotype, in which 17p13 deletions are not present, is characterised by growth delay, intellectual disability, seizures, *café au lait* skin spots, and minor facial

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dysmorphisms (Qazi *et al.*, 1979; Shashi *et al.*, 2003; Havlovicova *et al.*, 2007; Vazna *et al.*, 2008). A recent report stressed the similarity between the epileptic phenotype of the mild ring 17 chromosome syndrome and ring 20 chromosome syndrome (Ricard-Mousnier *et al.*, 2007). We report the first case, to our knowledge, of a girl affected by ring chromosome 17, with a normal general cognitive profile.

Case study

The patient is now a 17-year-old girl, with positive familial history for febrile convulsions in the paternal line. Perinatal and psychomotor development were normal. She is right-handed, with normal neurological examination and no facial dysmorphism. She has macrocephaly (occipito-frontal circumference in the 98th percentile and height in the 10th percentile) and five *café-au-lait* spots (ophthalmological examination was negative for Lisch nodules).

At 9 years, she began to present focal seizures clinically characterised by subjective cephalic sensation,

amaurosis, and aphasia. All the episodes occurred at awakening or during sleep, and lasted 2-3 minutes. In the postictal period, amaurosis could persist together with language impairment.

The interictal EEG showed normal background activity with epileptic abnormalities in the left temporal region; cerebral CT and MRI (at 10 and 14 years of age) were normal. At the age of 11 years, there were episodes of “non-convulsive status epilepticus” that lasted 2-3 days. These were characterised by headache, nausea, asthenia, transient aphasia, and right hand paresthesias. Prolonged video-EEG monitoring during these episodes showed continuous slow-and-spike activity in the left centro-temporal region (*figure 1*). This status was pharmacoresistant, as were the focal seizures. Between each episode of status, she also developed a depressive mood. She is now on valproate and lamotrigine with better control of the seizures that still persist monthly/yearly.

She never showed signs of intellectual disability. Neuropsychological follow-ups were regularly conducted, between 8 and 16 years of age, beginning from disease onset (at 8 years and 11 months, 9 years and 9

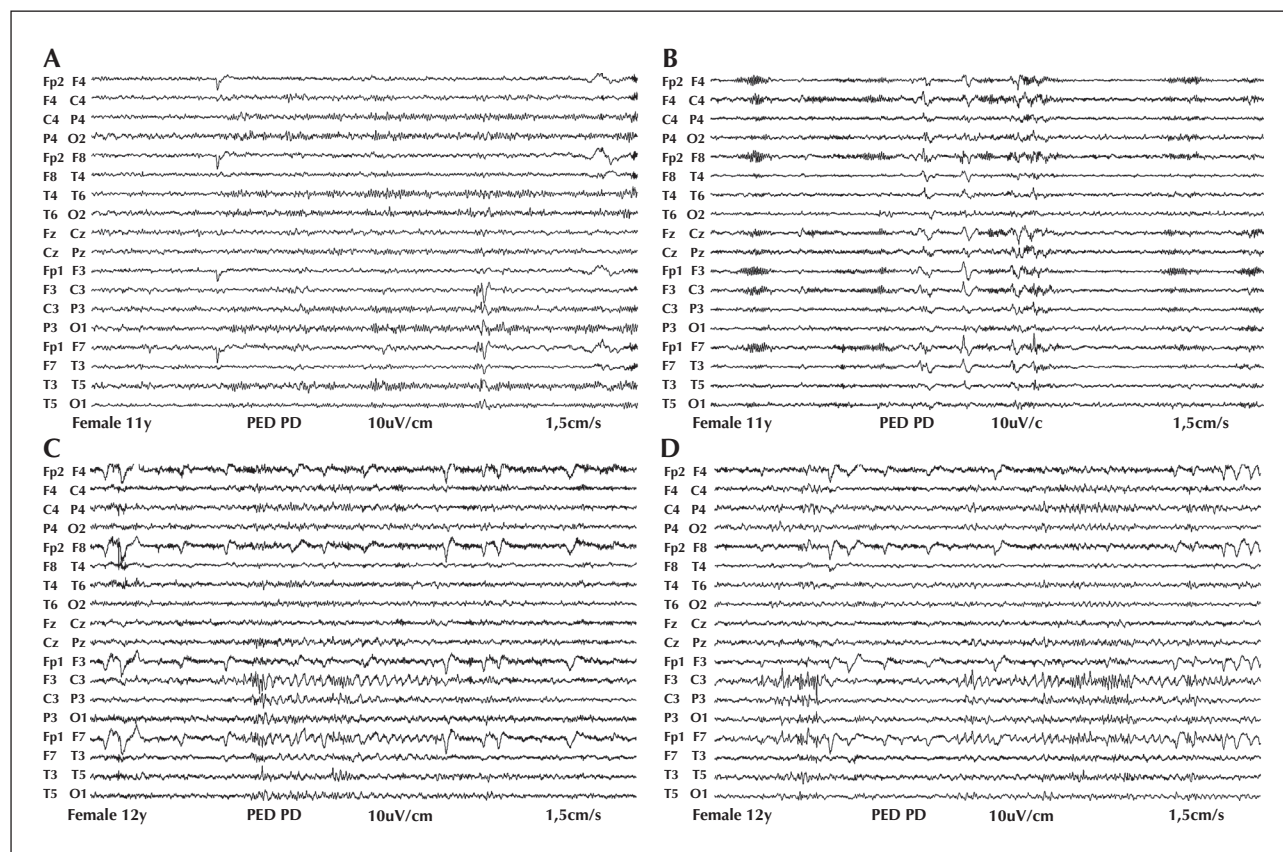


Figure 1. (A) Within normal background activity, there are polyspike and wave discharges that spread from the anterior temporal region to the entire perisylvian area. (B) During sleep (phase II) and wakefulness, the same abnormalities are found. (C and D) During non-convulsive status epilepticus, an almost continuous epileptic activity formed by a fast polyspike discharge, followed by rhythmic slow waves, is always evident in the left perisylvian region (with slight contralateral diffusion).

months, 12 years and 4 months, 13 years and 9 months, and 16 years and 11 months). Five cognitive domains were monitored: abstract reasoning, language, verbal memory, visuo-spatial abilities, attention, and executive functions. Analysis of the trend of standardised scores from tests (*table 1*) revealed that performance in abstract reasoning, short- and long-term verbal memory, as well as working memory tests were within the normative mean and stable over time. At 8 years and 11 months, she showed visuo-constructive and long-term visuo-spatial memory difficulties (assessed by the Rey complex figure copy). Almost one year later, scores in the visuo-constructive test fell within the normative mean. At 12 and 13 years, strategic lexical access (assessed by a phonemic fluency test) and task switching ability (assessed by the Trail Making Test B) test results were below the normative mean. On the other hand, planning skills (assessed by the Tower of London test) and visual search and visuo-motor speed (assessed by Trail Making Test A) were preserved. Importantly, at 17 years, all cognitive abilities were within normal range. Cytogenetic analysis performed on peripheral blood lymphocyte cultures revealed an abnormal karyotype characterised by the presence of

de novo ring chromosome 17 in 19% of metaphases: mos 46,XX,r(17)(p13q25)[19]/46,XX[81]. The array CGH (100 KB) showed no genetic deletion.

Conclusion

To our knowledge, this girl is the first reported patient affected by ring 17 syndrome with normal general cognitive functioning. This clinical peculiarity is probably due to the low degree of mosaicism of the aberration and the probable absence of deletion in the subtelomeric regions. The other main clinical features (*café-au-lait* spots, seizures, and partial growth delay) are consistent with the diagnosis of “mild” ring 17 syndrome (Surace *et al.*, 2009).

The peculiarity of this epilepsy phenotype is the coexistence of focal seizures and partial non-convulsive status epilepticus, both resistant to antiepileptic medication, as previously highlighted in ring 20 syndrome (Ville *et al.*, 2006; Vignoli *et al.*, 2009). Despite this similarity, the electroclinical correlations are quite different; ring 20 patients showed a widespread interictal and ictal bifrontal involvement, while our patient

Table 1. Longitudinal neuropsychological assessment.

Cognitive function/test	Age at follow-up				
	8 years 11 months	9 years 9 months	12 years 4 months	13 years 9 months	16 years 11 months
Abstract reasoning Raven's matrices ^{1,2}	0.90	0.20	1.51	0.43	0.26
Language					
Naming ^{2,3}	0.54	0.60	-0.10	-0.76	-1.15
Phonemic fluency ^{2,3}	-0.89	-1.20	-1.98	-2.34	-1.01
Semantic fluency ^{2,3}	-1.14	-0.75	-1.8	-1.00	-0.79
Verbal memory					
Forward digit span ^{2,3}	-0.72	-0.67	-1.33	-1.05	-0.94
Backward digit span ^{2,3}	0.15	0.2	1.12	0.43	0.53
Word list – Immediate recall ^{2,3}	1.93	1.82	1.57	-0.71	1.79
Word list – Delayed recall ^{2,3}	1.28	1.27	1.03	0.06	0.61
Visuo-spatial abilities					
Corsi's block test ^{2,3}	-0.75	0.25	0.73	0.72	-0.85
Rey complex figure - Copy ⁴	-3.55	-0.22	-1.55	-	1.90
Rey complex figure - Recall ⁴	-5	-1.00	0.18	-	0.61
Attention/Executive Functions					
Trail Making Test A (sec) ⁵	37	64	46	30	18
Trail Making Test B (sec) ⁵	125	127	147	95	75
Tower of London ⁶	0.48	1.92	1.24		-0.83

Z-scores are reported unless otherwise indicated. Scores below 2 standard deviations from the normative mean are in bold; scores between 1.5 and 2 standard deviations from the normative mean are marked in italics.

¹ Belacchi *et al.*, 2008; ² Gugliotta *et al.*, 2009; ³ Bisiacchi *et al.*, 2005; ⁴ Di Nuovo, 1976; ⁵ Scarpa *et al.*, 2006; ⁶ Sannio Fancello *et al.*, 2006.

showed mainly the implication of the left perisylvian and occipital areas. This is stressed by the presence of long hypomotor seizures with ictal and postictal amaurosis, right hand paresthesia, and postictal aphasia.

Interestingly, Vignoli *et al.* (2009) showed, in ring 20 patients, that the worsening of seizures was followed by cognitive deterioration, particularly in executive functions. In our patient, this characteristic was striking because the neuropsychological profile changed according to seizure presence/frequency. In particular, at 9 years, she showed visuo-constructive impairment but, as soon as seizures stopped, she showed prompt neuropsychological recovery. Later on, at 12 and 13 years old, she showed partial impairment of linguistic abilities, which improved during periods of better seizure control (*i.e.* at 17 years old; *table 1*). These findings strengthen, also, the idea that a posterior network, mainly left-sided, is involved.

Thus, our patient, as well as ring 20 patients, are good examples of how epileptic activity may alter neuropsychological functioning in the absence of any structural abnormalities (Vignoli *et al.*, 2009). In these cases, an aggressive treatment of the seizures probably prevents neuropsychological deficits.

The reason for this common epileptic behaviour, already highlighted by other authors (Ricard-Mousnier *et al.*, 2007; Surace *et al.*, 2009), is not known. The commonalities could depend on more than one reason; for example, similar genes could be deleted or duplicated in the subtelomeric regions or could be altered in their function by nuclear instability due to the malformation (Ricard-Mousnier *et al.*, 2007; Surace *et al.*, 2009). Certainly, new studies with high-density array CGH or extensive exome analysis will give further insight. Until now, array CGH has failed to identify any specific genetic locus, probably due to the low-grade mosaicism (Scott *et al.*, 2010) or the presence of only functional alteration of the subtelomeric region.

Due to the rarity of this chromosomal alteration, new insight into the pathophysiology will be provided by multicentric studies that can better define the genetic and phenotypic characteristics of this rare syndrome. As a conclusive remark, we advocate that, faced with a dramatic onset of focal seizures and the coexistence of focal status epilepticus, chromosome analysis, of at least 30 mitotic chromosome pairs (due to the possibility of mosaicism), is still warranted despite the absence of dysmorphic features, organ malformation, or intellectual disability (Vignoli *et al.*, 2009). □

Acknowledgements and disclosures.

We would like to acknowledge Dr Laura Cardarelli for performing the array-CGH test.

The authors have no conflict of interest to declare.

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TEST YOURSELF



- (1) Why might patients with “ring 17” and Miller-Dicker syndrome share common features?
- (2) When should chromosome analysis be performed?
- (3) Why is it important to have periodical neuropsychological follow-ups for patients with epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section “The EpiCentre”.