

Continuous spikes and waves during slow sleep in a child with karyotype 47, XYY

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ABSTRACT – The XYY syndrome is a sex chromosome aneuploidy occurring in one of 1,000 live male births. Only few data exist regarding the correlation between this syndrome and epilepsy. An EEG pattern suggestive of benign focal epilepsy with centro-temporal spikes has recently been described in four XYY patients. We report the first patient with XYY trisomy, rolandic spikes, and atypical evolution with continuous spikes and waves during slow sleep (CSWSS). The present report suggests that the association between an EEG pattern similar to that of BECTS and 47, XYY karyotype may not be coincidental. Moreover, we show that an atypical evolution with CSWSS may occur in this chromosomal disorder.

Key words: chromosomal disorder, CSWSS, centro-temporal spikes, seizure

The XYY syndrome is a sex chromosome aneuploidy occurring in one of 1,000 live male births (MacLean *et al.*, 1961). Subjects with this anomaly are often tall, impulsive and aggressive, and sometimes have severe acne, skeletal malformations, and mental deficiency (Ross *et al.*, 2012). Many studies found high prevalence of criminal behaviour and cognitive impairment in patients with XYY trisomy (MacLean *et al.*, 1961; Ross *et al.*, 2012), but there is little published data concerning a correlation between this syndrome and epilepsy (Volavka *et al.*, 1977; Torniero *et al.*, 2011; Bardsley *et al.*,

2013). The association between XYY trisomy and an EEG pattern suggestive of benign focal epilepsy with centro-temporal spikes (BECTS) has been described in four patients (Torniero *et al.*, 2011). Continuous spikes and waves during slow sleep (CSWSS) is an electrographic pattern characterised by nearly continuous spike-and-wave discharges during nREM sleep (Striano and Capovilla, 2013). According to an ILAE report, epileptic encephalopathy associated with CSWSS is an epileptic syndrome characterised by a combination of seizures and cognitive-behavioural impairment (Engel, 2006). However, most authors

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consider epileptic encephalopathies with an EEG pattern of CSWSS to represent a wide spectrum of epileptic conditions of different origins (Engel, 2006), that may include atypical BECTS and Landau-Kleffner syndrome. In this report, we describe the first patient with XYY trisomy and atypical benign partial epilepsy of childhood.

Case study

This only child of healthy, non-consanguineous parents was born at term after an uncomplicated pregnancy. At birth, he weighed 3,500 g (50th centile), length was 50 cm (50th-75th centile), and occipito-frontal head circumference was 34 cm (25th-50th centile). His psychomotor development was mildly delayed (first words at 18 months and independent walking at 24 months). At the age of 2 years, he started presenting sporadic seizures during both wakefulness and sleep, characterised by right hemiclonic jerks, sometimes evolving into generalised convulsions.

Different EEG recordings showed normal background activity along with spike-slow-wave complexes over left centro-parieto-temporal regions and vertex (figure 1), with activation during stage 1 and 2 of nREM sleep. At the age of 6, he came to our observation because of weekly seizures characterised by atypical absences and falls with loss of consciousness. Clinical examination revealed a long face, micrognathia, ectopic eruption of mandibular arch, long eyelashes, and dysarthria. EEG recordings showed typical centro-parieto-temporal spikes during wakefulness and continuous generalised spike-wave discharges occupying more than 85% of nREM sleep (figure 2). Psychological evaluation and psychometric examination (Wechsler scale) showed moderate intellectual disability (total IQ: 45; verbal IQ: 44; performance IQ: 47) and reduced attention span. Behavioural changes, in particular aggressiveness, became apparent a few months later. Brain MRI was normal. Karyotyping revealed 47, XYY. Seizures were resistant to different combinations of antiepileptic drugs including: phenobarbital, valproic acid, lamotrigine, ethosuccimide,

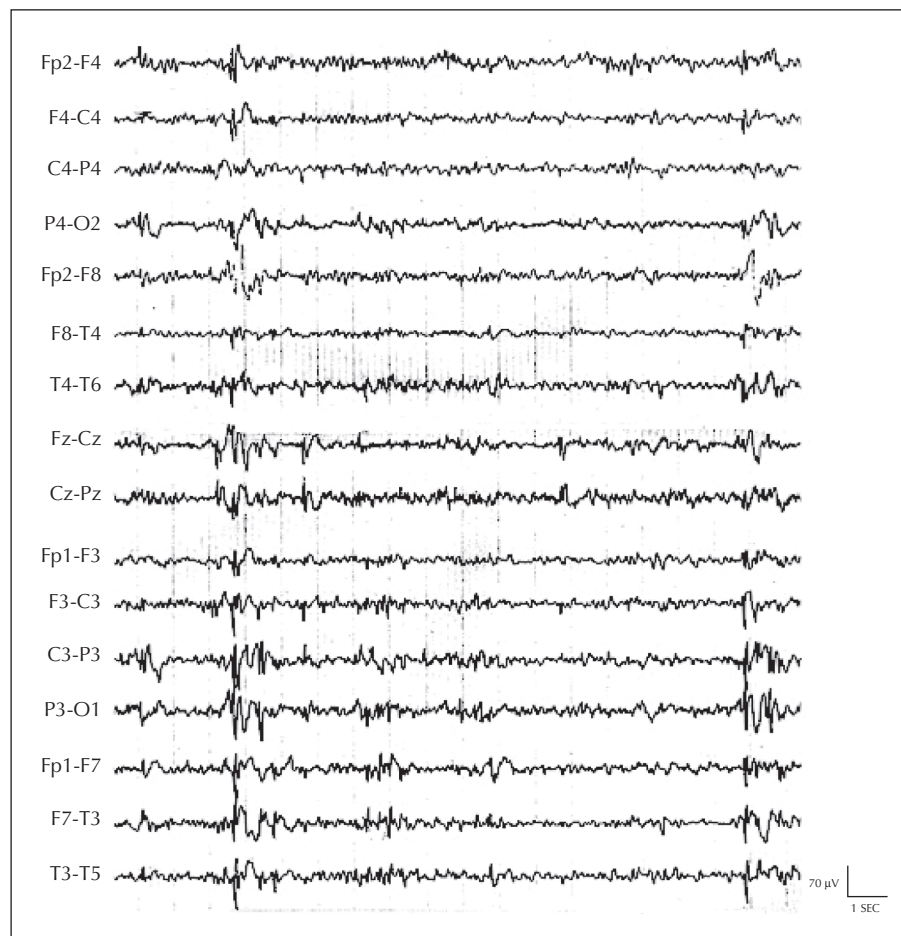


Figure 1. Mid-voltage spike-, polyspike-, and slow spike-waves were evident particularly over left parieto-temporal regions and vertex.

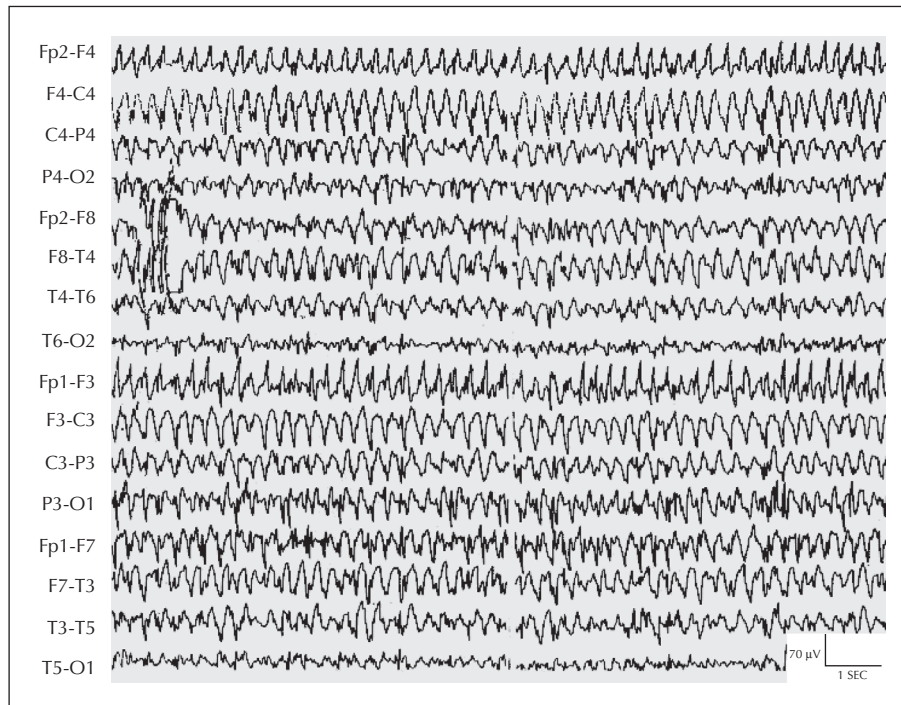


Figure 2. During sleep, continuous, diffuse spike-wave discharges were evident. No transient physiological sleep figure was evident.

topiramate, and clobazam. Monthly seizures and CSWSS persisted for two years. Neuropsychological examination performed one year later showed persistence of behavioural changes and attention deficit, as well as mild worsening of cognitive function (total IQ: 41; verbal IQ: 39; performance IQ: 43). Thereafter, the patient became seizure-free, EEG normalised, and antiepileptic drugs were stopped. At the age of 20, neuropsychological examination revealed elementary speech, reduced verbal fluency (verbal fluency test: 15; cut-off value: 27), and moderate intellectual disability (WAIS: total IQ: 55; verbal IQ: 53; performance IQ: 58; progressive Raven matrices: 15, cut-off: 17.5).

Discussion

To our knowledge, the association between karyotype 47, XYY and atypical benign partial epilepsy of childhood has never been reported. A recent, large cohort study (Bardsley *et al.*, 2013) found an increased prevalence of seizures in subjects with this aneuploidy, but further details were not reported. Torniero *et al.* described 4 patients with XYY syndrome and an EEG pattern similar to that of BECTS; of these, 3 had typical rolandic seizures while one never had seizures (Torniero *et al.*, 2011). These authors suggested that the association between this EEG pattern and XYY karyotype may not be random. Our observation indicates

that the association between an EEG pattern similar to that of BECTS and XYY karyotype may not be coincidental, and further shows that such patients may develop CSWSS and atypical benign partial epilepsy of childhood.

Atypical syndromes related to BECTS include: atypical benign partial epilepsy (defined by typical rolandic seizures in association with frequent atonic seizures and atypical absences, sometimes presenting as status epilepticus), CSWSS, Landau-Kleffner syndrome, and syndrome of opercular status epilepticus (Dalla Bernardina *et al.*, 2005). Aetiology, with the exception of cases with a known cerebral lesion, remains elusive. Recently, numerous *GRIN2A* mutations have been described in familial and sporadic cases of CSWSS, LKS, and atypical BECTS with language disturbances (Lesca *et al.*, 2013). A pathogenic role for these mutations seems possible, but the existence of asymptomatic carriers might suggest that they should be considered more as risk factors, rather than causative agents. To date, the question of whether such atypical syndromes in fact constitute a continuum together with typical BECTS or whether they are specific electro-clinical entities with a different origin, is still under debate (Dalla Bernardina *et al.*, 2005). In particular, CSWSS is usually associated with an insidious and progressive decline of neuropsychological state (Striano and Capovilla, 2013). It is believed that long-term neuropsychological outcome is also problematic and, overall,

normal language and intelligence is observed in only 10-40% of children (Striano and Capovilla, 2013). The age at onset, the duration of CSWSS, and localisation of interictal focus appear to play an important role in defining the type and degree of cognitive derangement. It has been postulated that the prolonged paroxysmal activity during sleep, as occurring in CSWSS, could interfere with the changes in slow-wave activity that normally occur in the course of sleep, and this may lead to impairment of cognitive functions and behaviour associated with CSWSS (Tassinari et al., 2000; Tassinari and Rubboli, 2006). In our patient, diffuse CSWSS appeared at age 6 and lasted for about two years. During this lifetime, he had severe behavioural changes and progressive worsening of cognitive function. Moreover, moderate intellectual impairment was still evident at the age of 20 years. Of course, both the chromosomal disorder and CSWSS may have contributed to the poor cognitive outcome in this patient. In conclusion, our case suggests that 47, XYY karyotype and a rolandic EEG pattern may be causally related, even if the pathophysiological relationship between these two conditions is not easy to explain. Moreover, we have shown that an atypical evolution with CSWSS may occur in patients with this chromosomal disorder. □

Disclosures.

None of the authors have any conflict of interest to disclose.

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