Pallister–Killian syndrome: an unusual cause of epileptic spasms

Rocio Sánchez-Carpintero* MD PhD; Ailsa McLellan MBChB MRCP MRCPCH, Great Ormond Street Hospital for Children NHS Trust, University College London, UK. Lucio Parmeggiani, Department of Developmental Neurosciences, University of Pisa and Research Institute Stella Maris Foundation, Italy. Annette E Cockwell BSc MSc DipRCPath, Wessex Regional Genetics Laboratory, Salisbury District Hospital, Wiltshire; Richard J Ellis BSc DipRCPath, Kennedy-Galton Centre, North West London Hospitals NHS Trust, Harrow; J Helen Cross MB ChB PhD MRCP(UK) FRCPCH; Susan Eckhardt, Great Ormond Street Hospital for Children NHS Trust, University College London, UK. Renzo Guerrini MD, Professor of Child Neurology and Psychiatry, Department of Developmental Neurosciences, University of Pisa and Research Institute Stella Maris Foundation, Italy.

*Correspondence to first author at Department of Paediatrics, Clínica Universitaria de Navarra, Universidad de Navarra, Avenida Pio XII, 36, 31080 Pamplona, Spain. E-mail: rsanchezc@unav.es

Pallister–Killian syndrome (PKS) is a rare, sporadic, genetic disorder characterized by dysmorphic features, learning disability*, and epilepsy. It is caused by a mosaic supernumerary isochromosome 12p (i[12p]). The i(12p) is infrequently present in peripheral lymphocytes but it is found in cultured fibroblasts and other tissues, such as bone marrow and lungs. Children present with peculiar dysmorphic features including coarse and flat facies, prominent forehead, scarcity of scalp hair over frontal and temporal regions, hypertelorism, broad nasal bridge, small nose with anteverted nostrils, highly arched palate, microretrognathia, cupid bow-shaped upper lip, and low-set ears (Hall 1983, Killian et al. 1983, Reynolds et al. 1987, Bielanska et al. 1996). A combination of these features, with severe to profound learning disability and epilepsy, characterizes the syndrome (Hall 1983, Reynolds et al. 1987, Warburton et al. 1987, Speleman et al. 1991, Bielanska et al. 1996).

Seizures have been reported in 40% of 67 cases (Bielanska et al. 1996) but their frequency is probably underestimated as most patients reported had a short follow-up (Reynolds et al. 1987, Warburton et al. 1987, Speleman et al. 1991, Bielanska et al. 1996). For the same reason, there is no information available on seizure semiology and electrophysiological correlates of epilepsy in these patients. We report two patients with PKS suffering from late onset epileptic spasms (ES).
Method
Both patients were diagnosed by medical genetics services to whom they were referred because of developmental delay and dysmorphic features. There was no history of neurological disorders or learning disability in any of the families. Patients were referred to Great Ormond Street Hospital for Children NHS Trust, London, UK, for study and follow-up of their epilepsy. Video–electroencephalogram (EEG) recordings were made in both patients. Development was estimated based on adaptive behavioural criteria (Sloan and Birch 1955). Written consent was obtained from the parents of patient 2 for publication of photographs.

Case reports
PATIENT 1
This 2-year-6-month-old male is the second child born to non-consanguineous parents. Pregnancy and delivery were normal. He presented at birth with dysmorphic features including upslanting palpebral fissures, sparse anterior scalp hair and sparse eyebrows, a long philtrum with thin and cupid-bow shape upper lip, and anteverted nostrils. Hypotonia and mild developmental delay were noticed during the first 2 years of life. Speech and language difficulties also became apparent in the third year of life. Peripheral blood chromosomes were normal, but mosaic tetrasomy 12p was demonstrated in fibroblasts (Fig. 1). Magnetic resonance imaging (MRI) of the brain was normal at age 2 years. Seizures began at the age of 2 years 4 months as symmetrical axial spasms occurring in series. Clusters lasted up to 10 minutes and occurred once or twice daily within an hour of awakening. Behavioural or cognitive deterioration was not noticed at any time. Clinically ES were characterized by a series of brief flexor spasms of the trunk with slight abduction of arms and flexion of hips, occurring every 3 to 7 seconds. The child was sometimes conscious during the series and distressed. Ictal EEG showed that each spasm was accompanied by a generalized spike followed by a triphasic slow wave (Fig. 2). Electromyographic correlates of the spasms consisted of a ‘diamond shape’ burst corresponding to a fast onset and a slower offset deltoid contraction.

There was slowing of background activity between spasms, but hypsarrhythmia was not observed. Interictal EEG showed slow background activity and bursts of generalized slow waves, in particular on eye closure and during drowsiness. Treatment with sodium valproate and vigabatrin monotherapies had no impact on the frequency of seizures. Carbamazepine led to worsening of spasms; a combination of vigabatrin and topiramate produced some improvement. At time of writing, spasms were replaced by partial seizures consisting of apnoea and slight stiffening, with subsequent loss of tone. These were self-limiting, short lived, and predominantly from sleep. In the seizures that occurred when the patient was awake he did have a warning – he would go to an adult – and retained awareness throughout.

Figure 1: Patient 1. Ideogram of partial karyotype showing additional isochromosome for short arm of chromosome 12.

Figure 2: Patient 1. Ictal electroencephalogram recording at age 2 years 6 months, showing a generalized spike followed by a triphasic slow wave. Two bottom electrodes show bilateral deltoid (R Delt, L Delt) muscle activity during spasm.

Figure 3: Patient 2 at age 10 months. Note sparse hair in frontal and temporal regions, upslanting palpebral fissures, long philtrum, cupid-bow shape upper lip, and microretrognathia.
Cytogenetic analysis
A normal male karyotype was found in 40 G-banded metaphases. However, the i(12p), which is associated with PKS, is not normally detected in peripheral blood metaphases. Subsequently, all 10 metaphases examined from a skin biopsy showed a male karyotype with an additional i(12p), which was consistent with the clinical diagnosis of PKS.

PATIENT 2
This 11-year-old female is the third child of healthy non-consanguineous parents. She was born at term after a normal pregnancy and delivery. Birthweight was 2.9kg and Apgar scores were 5 and 8 at the 1st and 5th minutes. At birth she was noticed to have a broad forehead, wide nasal bridge, small nose with anteverted nostrils, highly arched palate, edered lower lip, microretrognathia, and a short neck (Fig. 3). Early development was delayed and currently she has severe cognitive impairment. In addition, hypotonia, severe visual impairment, and mild hearing loss were noticed. An MRI of the brain at 18 months of age showed mild myelination delay and mild diffuse brain atrophy. Karyotype was normal in peripheral blood but tetrasomy 12p was demonstrated in cultured fibroblasts at 2 years of age. Daily clusters of periodic ES began at age 9 years 6 months. They presented as a series of symmetrical, brief, flexor spasms involving axial musculature and waking the patient in the first hours of sleep. There was no cognitive regression. Several clusters of ES were recorded with video–EEG. Clinically they were characterized by flexor contraction of the neck and trunk, sometimes accompanied by abduction of arms, occurring every 5 to 20 seconds for about 20 minutes. The child was conscious and severely distressed and afraid during the series of spasms. Ictal EEG showed a generalized slow wave at the beginning of each spasm followed by fast activity (Fig. 4). Interictal EEG showed normal background activity with occasional generalized bursts of slow spike and waves, with some emphasis over the posterior regions. Treatment with lamotrigine did not change seizure frequency. Clobazam at bedtime improved spasms only transiently.

Cytogenetic analysis
We analyzed G-banded karyotype of skin fibroblast cultures from the patient. Of 34 metaphase cells examined, 33 showed a female karyotype with an additional isochromosome derived from the short arm of chromosome 12. One single, normal, female cell was identified. The high number of cells with an isochromosome was not thought to be significant as the site of sampling may have had a high proportion of abnormal cells.

Discussion
These two patients with PKS experienced ES in a series, each series lasting from about 10 to 20 minutes. Although seizures are often mentioned in the description of PKS (Hall 1983, Killian et al. 1983, Reynolds et al. 1987, Warburton et al. 1987, Speleman et al. 1991), they are poorly described. ‘Generalized tonic-clonic seizures’ were reported in some patients (Hall 1983, Warburton et al. 1987, Speleman et al. 1991). ‘Staring spells followed by quick head and arm jerking lasting a few seconds’ were described in one patient and ‘myoclonic seizures’ in another (Reynolds et al. 1987). Both types of seizure could represent ES but they were not studied with video–EEG recordings. ES have not been reported in patients with PKS but they may be difficult to recognize, and they are easily mistaken for other types of seizure if documentation is not obtained.

ES are not unusual in patients with brain malformations including lissencephaly, tuberous sclerosis, hemimegalencephaly, and Aicardi syndrome (Arzimanoglou et al. 2004), and are frequently associated with other types of seizure, especially focal seizures (Gobbi et al. 1987). These two patients with PKS did not show specific structural abnormalities detectable on brain MRI. However, diffuse brain atrophy in patient 2 suggests the presence of cortical changes. ES have also been described in patients with other chromosomal abnormalities where cortical abnormalities are known to occur, such as Aicardi syndrome, Down syndrome, and Miller-Dicker syndrome (Arzimanoglou et al. 2004), and have been occasionally reported in patients with fragile X syndrome (Aicardi 1998), hypomelanosis of Ito, which is also a mosaic chromosomal disorder (Aicardi 1998) and, very rarely, in Angelman syndrome (Minassian et al. 1998). Cortical dysplasia, anomalies of dendrites, and alterations of regional cortical volumes have been observed in these syndromes.

Interictal EEG in our patients showed features consistent with symptomatic generalized epilepsy; however, these two patients were beyond the age range of West syndrome. EEG features in ES frequently reflect the underlying structural abnormality of the brain (Arzimanoglou et al. 2004).

ES are usually refractory to treatment (Gobbi et al. 1987). Indeed, multiple antiepileptic drug trials were ineffective in our patients. However, despite resistance to treatment, the spasms were not frequent enough nor part of a syndrome accompanied by cognitive regression that they were considered for steroid treatment.

PKS is a relatively rare chromosomal abnormality but needs

Figure 4: Patient 2. Ictal EEG recording at age 11 years. Several spasms are shown where a generalized slow wave is seen followed by fast activity. Two last electrodes show bilateral deltoid (R Delt, L Delt) muscle activity during spasms.
to be clinically suspected to address appropriate cytogenetic study of skin chromosomes. ES may occur in patients with this disorder, and symptoms could be subtle or easily mistaken for behavioural manifestations, so prompt diagnosis may be hindered if they are not recognized. In our patients with PKS, spasms had the usual characteristics seen in other developmental disorders of the brain, including late onset, persistence beyond infancy, and drug resistance. Clinicians should be aware of this possibility in PKS so that adequate diagnosis and treatment can be established.

DOI: 10.1017/S0012162205001623

Accepted for publication 28th April 2005.

Acknowledgements
R Sánchez-Carpintero was supported by a grant (EX 2001 33419023) from Ministerio de Educación, Dirección General de Universidades.

References


List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>Epileptic spasms</td>
</tr>
<tr>
<td>PKS</td>
<td>Pallister–Killian syndrome</td>
</tr>
</tbody>
</table>