Seizure Characteristics in Pallister–Killian Syndrome

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Pallister–Killian syndrome (PKS) is a congenital disorder attributed to supernumerary isochromosome 12p mosaicism. Craniofacial dysmorphism, learning impairment and seizures are considered cardinal features. However, little is known regarding the seizure and epilepsy patterns in PKS. To better define the prevalence and spectrum of seizures in PKS, we studied 51 patients (39 male, 12 female; median age 4 years and 9 months; age range 7 months to 31 years) with confirmed 12p tetrasomy. Using a parent-based structured questionnaire, we collected data regarding seizure onset, frequency, timing, semiology, and medication therapy. Patients were recruited through our practice, at PKS Kids family events, and via the PKS Kids website. Epilepsy occurred in 27 (53%) with 23 (85%) of those with seizures having seizure onset prior to 3.5 years of age. Mean age at seizure onset was 2 years and 4 months. The most common seizure types were myoclonic (15/27, 56%), generalized convulsions (13/27, 48%), and clustered tonic spasms (similar to infantile spasms; 8/27, 30%). Thirteen of 27 patients with seizures (48%) had more than one seizure type with 26 out of 27 (96%) ever having taken antiepileptic medications. Nineteen of 27 (70%) continued to have seizures and 17/27 (63%) remained on antiepileptic medication. The most commonly used medications were: levetiracetam (10/27, 37%), valproic acid (10/27, 37%), and topiramate (9/27, 33%) with levetiracetam felt to be “most helpful” by parents (6/27, 22%). Further exploration of seizure timing, in-depth analysis of EEG recordings, and collection of MRI data to rule out confounding factors is warranted.

How to Cite this Article:

INTRODUCTION

Pallister–Killian syndrome (PKS), also known as Pallister mosaic aneuploidy syndrome [Reynolds et al., 1987], is a rare sporadic disorder first described in adults in 1977 by Pallister [Pallister et al., 1977] and in children in 1981 by Killian and Teschler-Nicola [1981]. PKS is caused by the presence of a supernumerary isochromosome (i12p) which confers tetrasomy. The chromosomal anomaly is often absent in peripheral blood lymphocytes but is more frequently identified in cells cultured from skin fibroblasts or buccal mucosa [Bielanska et al., 1996]. Given the mosaic nature of the condition, genetic diagnosis is often elusive as karyotypes performed only on blood cells may fail to identify the condition [Horneff et al., 1993; Bielanska et al., 1996]. The PKS phenotype is typically described by the presence of three general findings: craniofacial dysmorphism, cognitive impairment [Stalker et al., 2006] (ranging from moderate to severe intellectual disability), and epilepsy.

The majority of existing literature on PKS has focused on reaffirming the craniofacial dysmorphisms (e.g., forehead prominence, temporal balding, and hypertelorism as shown in Fig. 1), associated congenital defects (e.g., diaphragmatic hernia, cleft palate, heart anomalies, etc.), physical exam findings (e.g., hypotonia and anomalous skin pigmentation) and genotypic variations observed [Smigiel et al., 2008]. Thus far, there does not appear to be a correlation between the proportion of tetrasomic cells and the severity of a patient’s clinical presentation (i.e., severity of congenital abnormalities, survival, and degree of cognitive impairment) [Schinzel, 1991; Speleman et al., 1991]. Exploration of the critical gene region of i12p responsible for PKS is ongoing.

In contrast to what is known about the epilepsy characteristics of other chromosomal disorders (e.g., Angelman [Minassian et al., 1998], Wolf–Hirschhorn (4p/C0) [Battaglia et al., 2009], inverted duplication 15 [Battaglia et al., 1997], terminal deletion 1p36

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Bahi-Buisson et al., 2008a,b) and ring chromosome 20 syndromes (Inoue et al., 1997), very little is known regarding the frequency of seizures, age of onset, typical seizure types, response to treatment or prognosis of epilepsy in PKS.

Prior case series and meta-analyses (Table I) suggest seizure prevalence in PKS to be in the vicinity of 42–59% (Bielanska et al., 1996; Stalker et al., 2006). However, these numbers are rough estimates, not to be mistaken for careful analysis of a particular symptom or disease process.

To date, only three groups (Table I) have described the detailed semiology and clinical characteristics of epileptic seizures in a total of five children with PKS (Sanchez-Carpintero et al., 2005; Yamamoto et al., 2007; Cerminara et al., 2010). Four of these children had onset of clustered epileptic spasms after infancy (“late-onset spasms”) and one of these children had an EEG consistent with “modified hypsarrhythmia.” Of these four children, one had onset of “massive myoclonic jerks” at age 13 months that appeared photosensitive in nature, and clustered tonic spasms only emerged later at age 4 (Cerminara et al., 2010). The last of these five children had onset of partial clonic seizures at age 5.5 years followed by the appearance of clustered tonic spasms in flexion 1 year later (Cerminara et al., 2010). This prior data, though based on a very small sample size, would suggest that children with PKS could be prone to later onset clustered spasms as a particular epileptic phenotype. Other case reports (Table I) suggest alternative seizure semiology. For example, Smigiel et al. [2008] reported uncategorized seizures in a neonate with PKS, while Speleman et al. [1991] described two patients with generalized seizures who were treated with valproic acid. Clearly, the existing information available with respect to the seizure and epilepsy characteristics in PKS (Table I) is limited and presented in a fairly inconsistent and fragmentary manner. This is because seizures were never before the focus of investigation as such. Further delineation of an epilepsy phenotype (or phenotypes) in PKS may aid in seizure diagnosis, improve anti-epileptic management, and provide a better understanding of prognosis for families and physicians (Battaglia et al., 2009).

In the present paper, we describe the seizure characteristics of 51 patients with PKS, the largest cohort of such patients to be evaluated for seizures and epilepsy to date. This was made possible via web-based contact and alliance with the family support group for people affected by Pallister–Killian syndrome [http://pkskids.net/].

**MATERIALS AND METHODS**

Fifty-one patients with a diagnosis of Pallister–Killian syndrome (39 males and 12 females), as confirmed by parent-reported chro-

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**TABLE I. Pallister–Killian Syndrome Seizure Literature Review—Comparison between Previously Reported Pallister–Killian Syndrome Patients and Our Cases**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Age at seizure onset</th>
<th>Seizure types (in decreasing order of frequency)</th>
<th>Medications used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerstner et al. [2008]</td>
<td>1</td>
<td>5 m</td>
<td>Focal myoclonias, atypical absence</td>
<td>OCBZ, VPA, TPM</td>
</tr>
<tr>
<td>Knab et al. [2008]</td>
<td>1</td>
<td>NR</td>
<td>“Seizure disorder”</td>
<td>CBZ, TPM</td>
</tr>
<tr>
<td>Smigiel et al. [2008]</td>
<td>1</td>
<td>Neonatal</td>
<td>NR</td>
<td>VPA, Vit B6</td>
</tr>
<tr>
<td>Yamamoto et al. [2007]</td>
<td>1</td>
<td>17 m</td>
<td>Flexor epileptic spasms</td>
<td>VPA</td>
</tr>
<tr>
<td>Stalker et al. [2006]</td>
<td>1</td>
<td>3 y</td>
<td>Febrile</td>
<td>VPA, CBZ, TPM, LMG, CLB</td>
</tr>
<tr>
<td>Sanchez-Carpintero et al. [2005]</td>
<td>2</td>
<td>2.3 y, 9.5 y</td>
<td>Symmetrical flexor spasms, focal</td>
<td>VPA, CBZ, TPM</td>
</tr>
<tr>
<td>Speleman et al. [1991]</td>
<td>3</td>
<td>9 y, 2 y, NR</td>
<td>Generalized</td>
<td>VPA</td>
</tr>
<tr>
<td>Reynolds et al. [1987]</td>
<td>11</td>
<td>Neonatal—4 y</td>
<td>Staring spells ± quick head jerks, myoclonic</td>
<td>PHB, DPH, VPA, CNZ, ESM</td>
</tr>
<tr>
<td>Cerminara et al. [2010]</td>
<td>2</td>
<td>13 m, 5.5 y</td>
<td>Myoclonic, partial, flex/extensor spasms</td>
<td>VPA, TPM, VGB, CBZ</td>
</tr>
<tr>
<td>Our cases, 2011</td>
<td>51</td>
<td>Mean 2 y 4 m (birth—12 y)</td>
<td>Myoclonic, generalized, infantile spasms, staring spells, complex partial</td>
<td>VPA = LEV, TPM, LTG = PHB</td>
</tr>
</tbody>
</table>

y, years; m, months; NR, not reported; CBZ, carbamazepine; CLB, clorazepam; CNZ, clonazepam; DPH, diphenylhydantoin; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; OCBZ, oxcarbazepine; PHB, phenobarbital; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; Vit B6, vitamin B6.
mosomal analysis, were included. Patients were identified initially via clinical contact, attendance at PKS support group meetings or by contact via notifications on the PKS Kids family web site [http://pkskids.net/].

**Inclusion Criteria**

1. Any patient presenting (or having presented within the past 20 years) to the pediatric neurology or pediatric genetics divisions at University of Utah Medical Center/Primary Children’s Medical Center with a diagnosis of Pallister–Killian syndrome was offered participation. In addition, patients/parents involved in the international PKS Kids organization, families of patients visiting the PKS Kids web site, and families attending the 2009 or 2010 annual PKS Kids Family meetings were offered participation.

2. Parent-reported genetic diagnosis of PKS (i.e., mosaic tetrasomy 12p as confirmed by fluorescence in situ hybridization, in fibroblast culture, or other tissue).

**Exclusion Criteria**

Patients (and their families) were excluded if the diagnosis of PKS had not yet been confirmed by chromosomal analysis (i.e., if their diagnosis was suspected purely based on clinical presentation).

Clinical details were obtained through a parent-based structured questionnaire which was handed, mailed, or emailed to parents of children with PKS. The questionnaire included (but was not limited to) questions regarding:

- Suspected/diagnosed seizure activity
- Age at onset of seizures
- Seizure type, frequency, timing (day/night/both), duration, triggers, clustering
- Occurrence of status epilepticus
- Need for hospitalization
- Seizure medications/therapies employed
- Current state of seizure disorder
- IQ/developmental age
- EEG/MRI results

Of note, precise delineation of seizure timing (e.g., while waking/awake/falling asleep/asleep, conditions which are not mutually exclusive in that patients can have seizures at multiple levels of alertness) was not distinctly elucidated, largely because the question pertaining to this information was only added into a later version of the survey. Direct parent interviews and/or phone/email contact with parents was employed in order to ascertain specific details not fully clarified in the initially completed survey (e.g., when a question was left blank or incomplete). Copies of pertinent medical records (e.g., EEG and MRI reports) were also requested and are still being collected at this time. As such, the EEG and MRI findings will not be discussed here. No incentives for participation were offered or provided.

Data from the collected surveys were summarized using descriptive statistics such as percentages, means, and standard deviations. Informed consent was obtained as the study involved voluntary provision of personal medical information and requested the option (which patients could refuse) of future contact by the investigators. The study was reviewed and approved by the Institutional Review Board of the University of Utah in Salt Lake City, UT.

**RESULTS**

The parents of 51 children with a confirmed diagnosis of PKS completed our survey. The median age of all patients at the time of study was 4 years and 9 months with a range of 7 months to 31 years (Table II). Seizures/epilepsy affected 27 of the 51 patients (53%). Amongst patients diagnosed with seizures, the mean age was 8 years and 4 months, with a range of 19 months to 31 years (Table III). An additional 10% of parents suspected that their child had seizures (Fig. 2). Taken together, 63% of patients in our cohort were identified as having confirmed or suspected seizures.

More than half of the patients diagnosed with seizures (56%) had seizure onset by 2 years of age, and nearly all of the patients with seizures (96%) had onset by 6 years (Fig. 3). The majority of the patients (63%) had seizures during both the day and night. Twenty-two percent of parents reported that their child had ever experienced status epilepticus. The most common seizure types noted in our cohort of children with PKS were (in decreasing order of frequency, as shown in Fig. 4) myoclonic (15/27, 56%), generalized convulsive (13/27, 48%), clustered tonic spasms (i.e., “infantile” spasms though usually occurring beyond infancy; 8/27, 30%), brief staring episodes (5/27, 19%), and complex partial seizures (3/27, 11%). Only one of the eight patients with clustered tonic spasms (“infantile spasms”) had spasm onset prior to 2 years of age. Nearly half of patients with seizures (13/27, 48%) had more than one seizure type.

Ninety-six percent of patients with seizures had ever taken antiepileptic medication with 56% having tried two or more (Table III). Sixty-three percent of patients with seizures remained on antiepileptic medication at the time of study. The most frequently used medications were valproic acid (10/27, 37%), levetiracetam (10/27, 37%), topiramate (9/27, 33%), phenobarbital (6/27, 22%), and lamotrigine (6/27, 22%; Fig. 5). The medications considered to be most helpful by parents were: levetiracetam (6/27, 22%), and phenobarbital, valproic acid, topiramate, and lamotrigine (2/27, 7% each).

<table>
<thead>
<tr>
<th>TABLE II. Selected Patient Characteristics</th>
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<tbody>
<tr>
<td>Total number of patients</td>
</tr>
<tr>
<td>Mean age at time of study</td>
</tr>
<tr>
<td>Median age at time of study</td>
</tr>
<tr>
<td>Age range</td>
</tr>
<tr>
<td>Number diagnosed with seizures</td>
</tr>
</tbody>
</table>

The EEG/MRI results

- IQ/developmental age
Including 51 patients with PKS, this is the largest cohort to date of patients with PKS to be evaluated for seizures and epilepsy. Our data confirm that seizures are a common occurrence in children with PKS, affecting more than 50% of children by age 2 years. Our total of 63% of patients with confirmed or suspected seizures is noticeably higher than some previously reported prevalence estimates (e.g., 42% noted by Bielanska et al. [1996]) but quite similar to that noted by Reynolds et al. [1987] in their case series of 10 patients and one stillborn fetus with PKS (i.e., 70%; also see Table I). The inclusion of many very young children in our cohort along with the broad spectrum of seizure types diagnosed and the suspicion (on behalf of parents) that their children have seizures which are not always formally diagnosed, suggest that seizures may be even more common than we report here. This emphasizes the importance of following this cohort into the future as well as the need to expand the awareness of practitioners in looking for seizures in their patients with PKS.

Although it has been previously suggested that most of the patients with PKS who are going to develop seizures do so shortly after birth [Schinzel, 1991], our data suggest otherwise as only eleven (35% or about one third) of the patients with seizures had seizures prior to 1 year of age and neonatal seizures were only reported in one child (2%). Likewise, our findings do support the notion suggested in the five previously described patients [Sanchez-Carpintero et al., 2005; Yamamoto et al., 2007; Cerminara et al., 2010 also see Table I] that late onset spasms (occurring after 1 year of age, and hence after the typical age of onset for “infantile spasms”) may represent a relatively common epileptic pattern for children with PKS. Although 22% of parents reported that their child had ever experienced status epilepticus, based on subsequent careful review of our survey data, we believe this number to be falsely elevated secondary to parental reporting of longer clusters of tonic spasms as continuous seizure activity. Our finding that 70%
(19/27) of our patients with seizures continued to have seizures despite 63% (17/27) remaining on anti-epileptic medication dem-
strates a presumed medication-refractory nature of seizures in PKS. In the absence of long term follow-up data, it is not possible to propose a single medication or specific regimen likely to be most effective for all or a majority of PKS children.

Unfortunately, the relatively young age of many of our patients limits our ability to accurately assess long-term prognosis in children with PKS. However, it is interesting to note that the two oldest patients studied (now aged 29 and 31 years) are currently seizure free. One of these two adults with PKS also appears to be one of the “higher-functioning” individuals in our cohort.

Epilepsy is a common symptom of many congenital and/or genetic syndromes that affect the nervous system. Some of these are associated with specific epilepsy or electroencephalographic patterns [Battaglia et al., 1997, 2009; Inoue et al., 1997; Minassian et al., 1998; Bahi-Buisson et al., 2008a,b]. For example, epilepsy is very common in children with Angelman syndrome and Wolf–Hirschhorn syndromes but differs substantially between the two. In the former, children often have mixed seizure types with frequent drop attacks and atypical absence seizures, accompanied by a characteristic EEG pattern described as periodic, large amplitude, slow spike-wave discharges often occurring in prolonged clusters or trains [Minassian et al., 1998; Korff et al., 2005; Valente et al., 2006; Conant et al., 2009; Thibert et al., 2009]. A fair percentage of these children will eventually go into remission [Uemura et al., 2005; Valente et al., 2006; Thibert et al., 2009]. In contrast, more than 90% of children with Wolf–Hirschhorn syndrome have epilepsy, but most have generalized tonic–clonic seizures and about half suffer episodes of status epilepticus. However, the majority eventually experience full seizure control or remission in childhood [Worthington et al., 2008; Battaglia et al., 2009]. Girls with Rett syndrome have a mixture of seizure types, but, perhaps similar to children with PKS, also have a variety of non-epileptic paroxysmal events which can confound management [Laan et al., 1998; Moser et al., 2007; Bahi-Buisson et al., 2008a,b; Buoni et al., 2008]. Finally, girls with Aicardi syndrome, experience early onset infantile spasms and typically suffer from lifelong, severe intractable epilepsy [Ohtsuka et al., 1993; Aicardi, 2005]. EEG patterns are very abnor-

mal, often exhibiting a so-called “split-brain” pattern [Ohtsuka et al., 1993; Aicardi, 2005].

Based on the above observations, we hypothesized that children with PKS may also exhibit some predictable epilepsy or seizure patterns. Our data so far, modestly support this hypothesis. As reported by parents, the seizure pattern/epilepsy syndrome associated with PKS is characterized by the following key elements: (1) absence of neonatal seizures; (2) onset by 2–5 years of age; (3) mixed seizure types with a predominance of myoclonic seizures and late-onset clustered tonic spasms (“late-onset infantile spasms” with onset at greater than 1 year of age); (4) rarity of convulsive status epilepticus; and (5) periods of relative refractoriness.

Although there does not appear to be a correlation between the proportion of tetrascopic cells and the severity of a patient’s clinical presentation, further examination of the scope of seizure severity within this population, when combined with genetic analysis, may shed light on the neurophysiologic mechanism of seizures in PKS. A longer term goal of our research is to identify optimal management strategies for the treatment of seizures in PKS. While we have limited information in this respect thus far, it appears that the majority of children diagnosed with seizures have required a trial of more than one AED. Though levetiracetam has been identified by parents as the most commonly effective single agent in this cohort, it is by no means consistently effective. No other AED stands out as the obvious second choice (see also Gerstner et al., 2008 for description of valproate-associated encephalopathy in a child with PKS). Only two patients in our cohort have required or been treated with the ketogenic diet. None had undergone vagal nerve stimulator im-
plantation. The latter two observations may speak to the relative lesser severity of the seizure phenotype in these children. Although our data do not yet allow us to firmly describe the long-term epilepsy prognosis of these patients, they do suggest that the overall severity of epilepsy in this population is relatively less than for children with Aicardi syndrome, or with other epileptic encephalopathies of childhood (such as Lennox–Gastaut syndrome, Myo-
clonic Astatic Epilepsy, or Dravet syndrome). The potential for remission may be less than that observed in Wolf–Hirschhorn syndrome, but better than for girls with Rett syndrome and certainly those with Aicardi syndrome.

Our survey-based study results are inherently limited by expec-
tation, recall and selection bias. Parents are not clinically trained to diagnose seizure activity and may over/under-report episodes. In addition, parents with a child with epilepsy were likely more motivated to fill out this questionnaire. Considerable variability with respect to parental interpretation of questions and terms was noted as well. For example, some parents could describe a seizure but not identify the category of seizure type. The differentiation between the duration of a single seizure versus a cluster of seizures was not always entirely clear. We have tried and intend to continue to address such potential obstacles by conducting a thorough medical record review down the road. That being said, a questionnaire-driven approach is particularly helpful in the case of rare diseases for which ascertainment of cohorts of substantial size is challenging [Bahi-Buisson et al., 2008a,b; Battaglia et al., 2009; Thibert et al., 2009; Cardoza et al., 2011].

In the future, a modified, more comprehensive survey aimed at capturing additional details pertaining to seizure timing and to
paroxysmal behaviors noted during sleep may be beneficial. An updated survey might also include questions regarding family history of epileptic seizures in order to remove this as a possible confounding factor.

An improved understanding of the epileptic patterns and seizure types associated with PKS, of their response to treatment and of their prognosis may provide the following benefits for patients with PKS and their families: (1) earlier recognition of seizures and seizure-like spells; (2) enhanced recognition of non-epileptic paroxysmal phenomena; (3) better prognostication; and (4) improved anticipatory guidance. Future correlation of seizure occurrence and pattern with genotype may help elucidate the neurophysiological underpinnings of epilepsy in PKS patients and could lead towards improved medical therapy. Finally, long term follow-up of the present cohort and in depth analysis of both EEG recordings (to confirm seizure types) and MRI data (to characterize common anatomical variations) will be essential to better clarification of prognosis over time.

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