Primary Amenorrhea in Pallister Killian Syndrome: Clinical Manifestation or Complication?

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Abstract: Pallister-Killian syndrome (PKS) is a rare genetic disorder caused by a mosaic tetrasomy of the short arm of chromosome 12 (12p). PKS has a wide spectrum of clinical manifestations which vary in different age groups. However, in the up to date literature there are no reported cases of puberty disorder associated with this syndrome. We describe a caucasian 17- year-old girl with PKS with primary amenorrhea as failure of appropriate pubertal progression.

Patient: at first general examination, the patient shows a phenotype compatible with the PKS of adulthood was noted. Auxological data revealed undernutrition (BMI ≤ z-score), with pubertal Tanner stage 3. A retarded bone age was detected. At pelvic ultrasound prepubertal uterus and microfollicular ovaries were noted. The laboratory data was compatible with hypogonadotropic hypogonadism.

Conclusion: this is the first case of primary amenorrhea in PKS. It would be interesting to reassess this novel finding in other patients affected by the same condition in order to establish whether hypogonadotropic hypogonadism is a typical clinical manifestation of the syndrome or it’s secondary to nutritional and stressful status.

Keywords: Primary amenorrhea, Pallister Killian syndrome, Undernutrition, Hypogonadotropic hypogonadism, Puberty.

INTRODUCTION

Pallister-Killian syndrome (PKS) is a rare, sporadic multisystem disorder caused by tetrasomy of the short arm of chromosome 12 presents in mosaic status. The prevalence of this condition is about 1/20,000-25,000 liveborn infants [1-4]. In some cases, PKS may be suspected before birth when second-trimester prenatal screening ultrasound reveals abnormalities or malformations such as diaphragmatic hernia or congenital heart disease [1-4]. The phenotype of younger children with PKS is well defined [5]. In neonatal period and early childhood the most common features are facial dysmorphism (such as prominent forehead, fronto-temporal alopecia, sparse scalp hair and eyebrows, hypertelorism, epicanthal folds, short nose with a flat nasal bridge, low-set ears, short neck, skin pigmentation defects, accessory nipples), a generalized muscular hypotonia, congenital anomalies and epilepsy. Instead, adolescent phenotype is more variable and differs from those of younger ones. A progressive psychomotor development delay with muscular hypertonia and contractures, a severe intellectual disability, hearing and ocular impairment are more prominent and typical in later childhood [4-7].

In the up to date literature there are no reported cases of puberty disorder associated with this syndrome probably because this condition is characterized by a poor life expectancy. However, nowadays, thanks to medical assistance improvement, an increase in the life expectancy of patients with PKS has been recorded [4].

We described a 17- year-old girl with PKS in which primary amenorrhea, as failure of appropriate progression of puberty, was recorded.

CASE-REPORT

G., a caucasian 17-year-old female suffering from PKS, comes to our attention for respiratory failure due to pneumonia. Treating the acute event a multidisciplinary re-evaluation of her basic clinical condition is conducted and a primary amenorrhea is recorded.
The patient was born at full term by eutocic delivery, with birth appropriate for gestational age (birth weight 3570 gr). At the prenatal ultrasound, several abnormalities had been detected, however the chorionic villus sampling and the genetic counselling had not been conclusive. The diagnosis (karyotype on dermal fibroblast culture [47XX+I(12)]) was performed at birth due to the presence of multiple malformations (sagittal suture diastasis, sui generis facies, abnormal finger implantation, femoral shortness and axial hypotonia with flexor spastic hypertonia of the limbs). Her medical history highlights non-inbred parents, no familiarity with hereditary diseases and delayed pubertal onset.

The perinatal period was characterized by a difficult adaptation to extrauterine life (Apgar 2-6-7) with severe respiratory depression. For the perinatal suffering associated with the onset of epileptic seizures, a brain magnetic resonance imaging was performed, showing a hypoplastic right cerebral hemisphere and a left hemisphere with a parenchymal lesion, probably due to a perinatal hemorrhage-ischemia. Supratentorial ventricular system was larger than normal and even the electroencephalogram trace was pathological (very poor trace, no differentiation in phases). Antiepileptic drugs were used.

At our first general examination, we noted a phenotype compatible with the PKS of adulthood: pale skin, elongated facies, macroglossia and oral breath. Panniculus adiposus poorly represented. The osteo-muscular system is characterized by severe skeletal deformities partly by spastic tetraparesis, partly by severe scoliosis and partly by congenital deformities. Cardio-thoracic and abdominal objectivity are within normal limits, with the exception of the left hemithorax, which appears hypoventilated due to the severity of the scoliosis. A significant cognitive delay associated with a severe postural spastic tetraparesis was also noted.

Auxological data showed weight 28.3 Kg (z-score CDC: -8.44), length 145 cm (z-score CDC: -2.80) [8], BMI 13.5 kg/m² (z-score CDC: -4.9) [8], knee height 45

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Value</th>
<th>Reference Value</th>
</tr>
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<tbody>
<tr>
<td>TSH</td>
<td>2.14 mUI/L</td>
<td>0.2-7.6 mUI/L</td>
</tr>
<tr>
<td>FT3</td>
<td>2.67 pg/ml</td>
<td>2.50-4.64 pg/ml</td>
</tr>
<tr>
<td>FT4</td>
<td>0.84 ng/dl</td>
<td>0.7-1.7 ng/dl</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>0.1 micromol/L</td>
<td>0.01-0.03 micromol/L</td>
</tr>
<tr>
<td>DHEA</td>
<td>0.06 micromol/L</td>
<td>0.008-0.02 micromol/L</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>0.2 ng/ml</td>
<td>0.8-2.4 ng/ml</td>
</tr>
<tr>
<td>17-OH-progesterone</td>
<td>0.19 ng/ml</td>
<td>&lt; 0.2 ng/ml</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.03 ng/ml</td>
<td>0.2-0.38 ng/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>1.1 m UI/ml</td>
<td>1-9.2 mUI/ml</td>
</tr>
<tr>
<td>LH</td>
<td>0.6 m UI/ml</td>
<td>0.4-11.7 mUI/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>25.4 ng/ml</td>
<td>&lt;25 ng/ml</td>
</tr>
<tr>
<td>17 beta-estradiol</td>
<td>&lt;5 pg/ml</td>
<td>15-350 pg/ml</td>
</tr>
<tr>
<td>PTH</td>
<td>22.5 pg/ml</td>
<td>9-52 pg/ml</td>
</tr>
<tr>
<td>Cortisol</td>
<td>5 ng/ml (steroid use)</td>
<td>20-90 ng/ml</td>
</tr>
<tr>
<td></td>
<td>59 ng/ml (steroid suspension)</td>
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<tr>
<td>IGF-1</td>
<td>368 ng/ml</td>
<td>123-546 ng/ml</td>
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<td>ACTH</td>
<td>37 pg/ml</td>
<td>7.2-63 pg/ml</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>121 pg/ml</td>
<td>2-200 pg/ml</td>
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</table>
Pallister-Killian syndrome is an extremely rare syndrome with a wide spectrum of clinical manifestations [1, 4]. To our knowledge, this is the first case of primary amenorrhea in PKS; the patient developed a failure of appropriate progression of puberty.

Delayed puberty (DP) is widely described in literature in pediatric patients suffering from chronic disease [16]. As in our patient, in this population DP may have a multifactorial etiology. First of all, it’s known that an adequate and balanced healthy diet in all phases of the growth is necessary for the onset and the achievement of a complete pubertal stage and reproductive competence [17, 18]. In time undernutrition may also alter secretion of GH-IGF1 axis and act on the synthesis and release of leptin that seems to have a role as a trigger for the onset of puberty [16, 19]. In our girl, clinical and biochemical signs of undernutrition due to an inappropriate dietary energy intake and nutrient losses related to neurological impairment and her disabling dysphagic symptoms were detected; these data confirm the crucial role of the nutritional status on the regular secretion of hypothalamic gonadotropins, ovarian stimulation and menarche in adolescence.

Additionally, over the years the patient has had to face many respiratory complications and a wide spectrum of recurrent infections due to her fragile condition causing an inappropriate responsiveness of the stress system CRH-ACTH-cortisol which has likely impaired girl’s growth and pubertal development.

A condition of chronic inflammation with release of inflammatory cytokines involved in possible retardation of growth and progression of puberty may be also considered [16]. Furthermore, these patients are subjected to a cumulative chronic stress that induces the activation of the hypothalamic-pituitary-adrenal pituitary axis resulting in suppression of hypothalamic-pituitary-gonadal axis with consequent decrease in LH secretion [18, 20].

The role of structural brain abnormalities or malformations and of her chronic therapy [17, 21] could not be excluded. As reported in literature pubertal disorders are frequently noted in patients in polytherapy and in particular, glucocorticoids and anticonvulsants may impact several systems involved in controlling and releasing of hypothalamic gonadotropins [15, 22]. Most frequently pediatric patients with brain damage and under antiepileptic therapy show precocious puberty but also delayed puberty, as in our case, has been described [22, 23].
This novel finding described in G. should be reassessed in patients affected by PKS. Further research is recommended to establish whether hypogonadotropic hypogonadism is a characteristic manifestation of the syndrome or secondary to multiple risk factors, including nutritional status, high allostatic load, assumption of drugs.

REFERENCE


