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

Luisa Abbattista[1,2,#], Paola Baldassarre[1,2,#], Roberta Grazi[1,2,#], Valeria Calcaterra[1,3,*], Patrizia Carlucci[1], Valentina Fabiano[1,2], Paola Erba[1], Elvira Verduci[1,4] and Gianvincenzo Zuccotti[1,2]

[1]*Pediatric Department, "Vittore Buzzi" Children's Hospital, 20154 Milan, Italy*

[2]*Department of Biomedical and Clinical Science "L. Sacco", University of Milan, 20157 Milan, Italy*

[3]*Pediatric and Adolescent Unit, Department of Internal Medicine, University of Pavia, 27100 Pavia, Italy*

[4]*Department of Health Sciences, University of Milano, 20142 Milano, Italy*

**Abstract:** *Introduction:* 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 ≤3 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.

*Address correspondence to this author at the Pediatric and Adolescent Unit, Department of Internal Medicine, University of Pavia, Via Aselli 2, 27100 Pavia, Italy; Tel: +39 0382 986356 - 987586; E-mail: valeria.calcaterra@unipv.it

#Equal contribution.

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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/m$^2$ (z-score CDC: -4.9) [8], knee height 45

**Table 1: Hormonal Parameters**

| Hormones | Value | Reference Value |
|---|---|---|
| TSH | 2.14 mUI/L | 0.2-7.6 mUI/L |
| FT3 | 2.67 pg/ml | 2.50-4.64 pg/ml |
| FT4 | 0.84 ng/dl | 0.7-1.7 ng/dl |
| DHEA-S | 0.1 micromol/L | 0.01-0.03 micromol/L |
| DHEA | 0.06 micromol/L | 0.008-0.02 micromol/L |
| Androstenedione | 0.2 ng/ml | 0.8-2.4 ng/ml |
| 17-OH-progesterone | 0.19 ng/ml | < 0.2 ng/ml |
| Testosterone | 0.03 ng/ml | 0.2-0.38 ng/ml |
| FSH | 1.1 m UI/ml | 1-9.2 mUI/ml |
| LH | 0.6 m UI/ml | 0.4-11.7 mUI/ml |
| Prolactin | 25.4 ng/ml | <25 ng/ml |
| 17 beta-estradiol | <5 pg/ml | 15-350 pg/ml |
| PTH | 22.5 pg/ml | 9-52 pg/ml |
| Cortisol | 5 ng/ml (steroid use)<br>59 ng/ml (steroid suspension) | 20-90 ng/ml |
| IGF-1 | 368 ng/ml | 123-546 ng/ml |
| ACTH | 37 pg/ml | 7.2-63 pg/ml |
| Aldosterone | 121 pg/ml | 2–200 pg/ml |

cm (<3 percentile) [9][10], upper arm girt 16 cm (<5°c.le CDC) [11, 12], height based on body segment lengths according to Stevenson's method [13] 168 cm (z-score CDC: 0.79. Target height 163.5 cm) Oral feeding was adopted. Tanner pubertal stage was 3 for breast and pubic hair [14]; onset of puberty has been reported around 11 years old, with failure of appropriate progression.

Hand and wrist radiography showed retarded bone age between 13 and 14 years (using the Greulich and Pyle atlas). At pelvic ultrasound total uterine length was 4.8 cm with fundus equal in size to cervix and microfollicular ovaries (ovarian volume 2.6 and 2.5 cc, respectively) were detected.

As reported in Table **1**, hormonal pattern showed normal thyroid function and prolactin value. Normal adrenal function was recorded, except to a low cortisol level due to steroid use to treat respiratory infection, with successive normalization after suspension. Celiac disease and/or inflammatory bowel disease were excluded. A hypogonadotropic hypogonadism was supposed. Due to the severity of clinical status, the luteinizing-hormone releasing hormone (LHRH) stimulation testing was not performed.

In biochemical analysis, low levels of prealbumin (0.18 g/L, normal value 0.2-0.4) and vitamin D (6.6 ng/ml, normal value ≥30) were depicted with normal values of calcium, phosphorus, lipid profile, folate, vitamin B12, plasma amino acid. Blood count was normal with the exception of thrombocytopenia (43000-130000/mmc), known from birth and probably related to PKS.

A tailored nutritional intervention was planned.

## DISCUSSION

Puberty is defined as the transition period from childhood to adulthood [15]. It is characterized by the attainment of adult height and body composition, skeletal maturation and secondary sexual features, psychosocial maturation and reproductive capacity [15]. In girls, menarche is a late puberty marker. Primary amenorrhea is defined as the absence of menarche in ≥15-year-old females with developed secondary sexual features and normal growth or in ≥13-year-old females without signs of pubertal development; primary amenorrhea should be also considered as the absence of menarche 3 years after thelarche or 5 years after thelarche, if that occurred before the age of 10 years [15].

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 be not 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.

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