First trimester diagnosis of Pallister-Killian Syndrome in a fetus with suggestive abnormalities.

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Dignostic au premier trimerstre du syndrome de Pallister Killian chez le fœtus suspect d'anomalies

LA TUNISIE MEDICALE - 2010 ; Vol 88 (n°09) : 666 - 669

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RÉSUMÉ

Prérequis : Le syndrome de Pallister Killian est une anomalie chromosomique rare et sporadique caractérisée par une tétrasomie 12p souvent en mosaïque. C'est seulement en 2000 que le premier cas du Synndrome de Pallister Killian a ètè diagnostiqué lors de l'exploration d'une hyperclarté nucale.
But : Rapportons une nouvelle observation
Cas clinique : Nous rapportons le cas d'un diagnostic précoce du syndrome de Pallister Killian évoqué devant l'association d'une clarté nucale épaisse, d'une hernie diaphragmatique, d'une dysmorphie faciale typique ainsi qu'une micromélie à prédominance rhizomélique. La biopsie trophoblastique a montré un caryotype normal. L'analyse cytogénétique du liquide amniotique à l'amniocentèse a posé le diagnostic.
Conclusion : Les principaux signes échographiques en faveur du SPK sont : Hydramnios, hernie diaphragmatique congénitale (CDH) et une micromelie rhizomélique. L'anasarque, l'hygroma coli ou l'hyperclarté nucale (HCN), macrosomie fœtale, ventriculomégalie ou la présence d'un appendice sacral sont moins communes. L'amniocentèse avec étude du caryotype est considérée comme le gold standard pour le diagnostic du PKS.
Une étude morphologique minutieuse au premier trimestre à la recherche d'anomalies échographiques hautement évocatrices du syndrome de Pallister Killian, peut orienter l'étude cytogénétique.

Mots-clés
Syndrome de Pallister Killian; isochromosome 12p; clarté nucale augmentée, hernie diaphragmatique

SUMMARY

Background: Pallister-Killian Syndrome is a rare, sporadic chromosomal disorder characterized by a tetrasomy 12p often in mosaic. It is only in 2000 that the first case of PKS was diagnosed in the first trimester further to an increased nuchal translucency
Aim : Report a new case
Case report : To our knowledge, we present the first case of early prenatal diagnosis of Pallister Killian Syndrome due to the presence of an increased nuchal translucency, a diaphragmatic hernia, a typical facial dysmorphism and a micromelia of a predominantly rhizomelic type . A chorionic cells biopsy showed a normal karyotype. The diagnosis was revealed on cytogenetic analysis of amniotic fluid sampling.
Conclusion : The main ultrasound indicators of PKS seem to be: Hydramnios, congenital diaphragmatic hernia (CDH) and a micromelia of a rhizomelic type. The Hydrops fetalis, hygroma coli or increased nuchal translucency (INT), fetal overgrowth, ventriculomegaly and presence of a sacral appendix are less common. The amniocentesis with the study of the karyotype on amniotic cells is considered to be the gold standard for the diagnosis of PKS.
A good morphological study during the first trimester in search of ultrasound abnormalities highly suggestive of PKS is able to direct the cytogenetic study.

Key-words
Pallister-Killian syndrome; isochromosome 12p; increased nuchal translucency; diaphragmatic hernia.

Pallister-Killian Syndrome (PKS) is a rare, sporadic chromosomal disorder. It was first described by Pallister et al in 1977 in two adult patients (1). In 1981, Wolfgang Killian described four other cases (2). PKS is characterized by a tetrasomy 12p often in mosaic. The first prenatal diagnosis was reported by Gilgenkrantz et al in 1985 (3). Since this publication, about 60 cases of prenatal diagnosis have been reported in the setting of a screening program for common chromosomal aneuploidies or when discovering fetal malformations. It is only in 2000 that the first case of PKS was diagnosed in the first trimester further to an increased nuchal translucency (INT).

To our knowledge, we present the first case of early prenatal diagnosis of PKS due to the presence of an INT, a diaphragmatic hernia (DH), a typical facial dysmorphism and a micromelia of a predominantly rhizomelic type.

The objective of this work is to show that suspicion of PKS prior to karyotyping is advantageous in order to plan sampling of more than a single fetal tissue. A good morphological study during the first trimester in search of ultrasound abnormalities highly suggestive of PKS is able to direct the cytogenetic study.

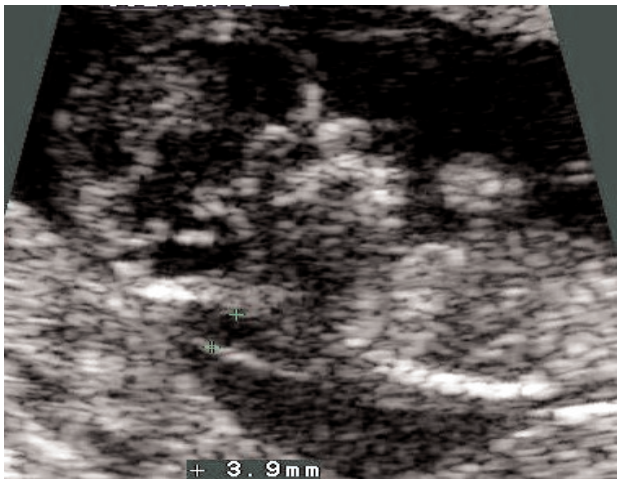
CASE REPORT

A 30-year-old woman, gravida 2 para 0, was referred to our center for prenatal care because of INT. The family history was unremarkable and the parents were unrelated.

Our scan, performed at 13 weeks showed several abnormalities:

- INT: 3.9mm. (Figure 1). CRL= 64 mm

Figure 1 : US at 13 weeks showing abnormalities



• A diaphragmatic hernia demonstrated by the ascension of the stomach and small bowel within the thorax with a cardiac displacement to the right. However, it is interesting to notice that abdominal perimeter was in the 50-th percentile which did not suit to the diagnosis of DH. This can be explained by the fact that, in this term, internal herniated organs are not rather voluminous. (figure 2, 3)

Figure 2 : Internal herniated organs

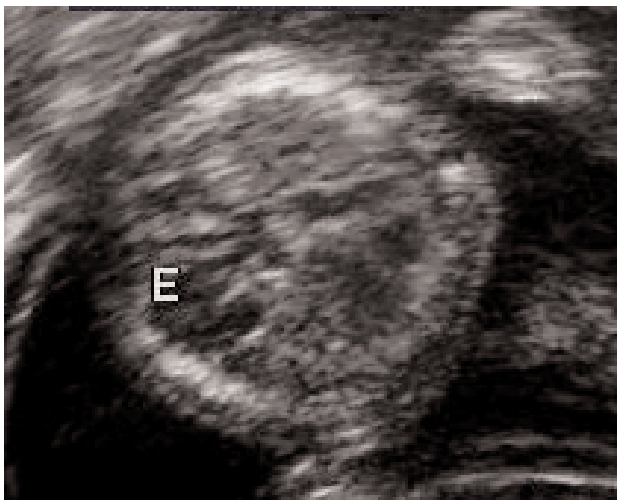
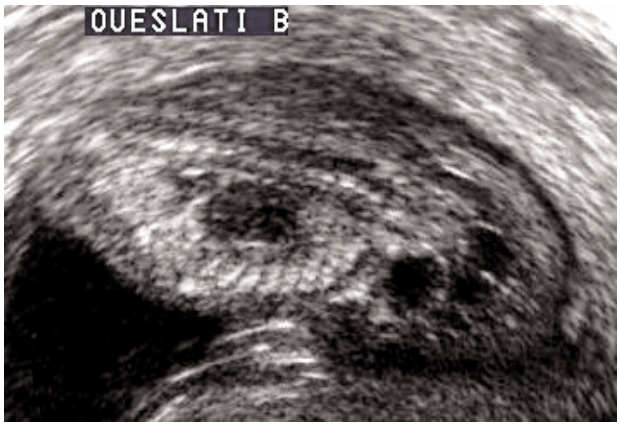
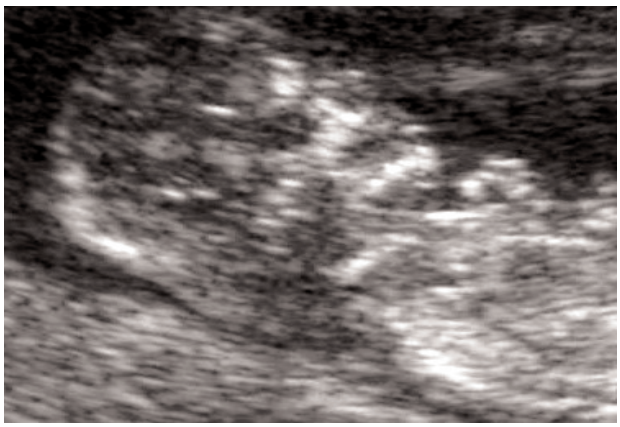


Figure 3 : Internal herniated organs



• A suggestive facial dysmorphism: a long and convex philtrum and a slightly prominent
forehead. (figure 4)

Figure 4 : Facial dysmorphism



• A moderated micromelia of a rhizomelic type prevailing especially on the humerus (table
1). Furthermore, the hands of the fetus were wrinkled and boots.
• Besides we noticed that the big cistern seemed "too wide "; even though we do not arrange at present of normal measurements of the big cistern in the first trimester.
• We did not notice any heart defects and the ductus venosus flow was normal.

In front of these ultrasound abnormalities, several diagnoses were particularly evoked: T18, T13, T21, and especially PKS but also Fryns syndrome...

A Chorionic cells biopsy was performed. The culture was long and revealed a normal Karyotype. Now, and it is ail the interest of the premature morphological study, the association of these suggestive abnormalities (DH, facial dysmorphism, moderate micromelia) leads us to counsel the couple for an amniocentesis. Cytogenetic analysis revealed male karyotype with a supernumerary chromosome consistent with an isochromosome 12p unbalanced by the presence of a tetrasomy of the short arm of the chromosome 12. Owing to this cytogenetic result, the parents opted to terminate the pregnancy.

The postmortem examination revealed a male fetus consistent with 17-18 weeks of age with marked and diffuse edema. Hypertelorism was noted with a wide and flat nasal bridge, a simple and elongated Philtrum, an orbital palate, low set and dysplastic ears. The neck was short and webbed with excess nuchal skin. Disproportionate shortness of the upper and lower extremities was reported. (Short Upper limbs < 5.6cm, Lower limbs: 6.7 cm). Index in tongs in the left hand, campodactyly to the right, distal phalanxes were very short. The distance between the first and the second toes was enlarged.

During the autopsy, the basic structures of the brain were present. A Hydrocephaly was noted with a hypoplasic cerebellum. A left diaphragmatic defect (1.5 cm in diameter) was also present. The thorax contained the intestinal handles, the stomach, the pancreas, the spleen, the left lobe of the liver. The left lung was hypoplasic and diverted to the right. The heart was displaced to the right, its autopsy showed a tetralogy of fallot. The bladder was well-developed. No renal malformations were observed. A Small Scrotum was noted with undescended testes.

The radiological examination revealed a brachycephaly and a femur of 21 mm (« 5th Percentile) (table 1).

Table 1 : Foetal biometry (in mm, Fc, BPM)

13SA	LCC	BIP	PC	PO	Fem	Hum	FC
	64,2	22,7	89,5	62,9	7	5,8	161
Centils	20è p	65èp	70è p	50è p	3è p	4è p	60è p

DISCUSSION

PKS is rare, but its frequency is probably underestimated because of its tissue-specific distribution and wide spectrum of abnormalities 4. To our knowledge, we present the first case of early prenatal diagnosis of PKS due to the presence of an INT, a diaphragmatic hernia (DH), a typical facial dysmorphism and a micromelia of a predominantly rhizomelic type. The diagnosis was made on cytogenetic analysis of amniotic fluid sampling.

PKS is cytogenetically characterized by a mosaic tissue-specific distribution of an extra 12p isochromosome. Its fraction is greatly decreased in the fetal blood cells compared with that of the amniotic cells and fibroblasts. Hence, suspicion of PKS prior to karyotyping is advantageous in order to plan sampling of more than a single fetal tissue. At present, Culture of amniotic fluid cells is the optimal method, in which extra chromosome 12p mosaicisme is detectable with high reliability 5. The most common indications are ultrasound abnormalities and advanced maternal age6,7,8. The main ultrasound indicators of PKS seem to be: Hydramnios, congenital diaphragmatic hernia (CDH) and a micromelia of a rhizomelic type. The Hydrops fetalis, hygroma coli or increased nuchal translucency (INT), fetal overgrowth, ventriculomegaly and presence of a sacral appendix are less common 4,9. When sonographic abnormalities were found the mean gestational âge was 22 weeks 4.

Langford 10 presented in 2000 the first case of PKS diagnosed further to an INT at 13 weeks of gestation. Prenatal diagnosis was performed by chorionic villus sampling. The sonographic examination performed at 15 weeks revealed a diaphragmatic hernia, a hypoplasic left heart as well as a postaxial polydactyly. Abad described a case of PKS with an INT and a complex heart disease 11. Kim described, in 2008, two other cases with an INT 4. So, we present the fifth case of PKS diagnosed during the first trimester with an INT, but contrarily to the previous cases, we also objectified early suggestive ultrasound abnormalities: diaphragmatic hernia, facial dysmorphism, micromelia of a rhizomelic type. Furthermore, we noticed that the INT was compartmentalized into bags evoking us likely evolution towards a hygroma coli. This observation was also found in the literature 4 .

Although prenatal diagnosis of PKS is often difficult, it is essential for genetic counseling as there is no risk of recurrence (for Fryns syndrome the risk is of 25%). In order to avoid misdiagnoses, Doray et al. proposed some guidelines for PKS prenatal diagnosis. Polyhydramnios, congenital diaphragmatic hernia and rhizomelic micromelia in a eutrophic or overgrowth fetus are highly suggestive of tetrasomy 12p. The absence of ultrasound anomalies or the presence of non-specific minor anomalies constitute the main causes of failures of prenatal diagnosis of PKS. In these cases, a careful sonographic examination of the fetal face, as suggested by Paladini et al. 12, might contribute to directing the diagnosis towards PKS. Indeed, the association between a small nose, a thin upper lip with a protruding lower one and represents an important marker of PKS which has several advantages: First, it can be detected at early ultrasound, as demonstrated by the present case report. Second, it can be considered a fairly constant indicator of the syndrome; and finally, it is usually not associated with Fryns syndrome, which represents the main differential diagnosis of PKS. In fact, in Fryns syndrome the most common dysmorphic

facial features include micrognathia and cleft lip and/or palate. Neither of these anomalies are commonly associated with PKS, in which only micrognathia can occasionally be found. On the contrary, hypertelorism is frequent in PKS and rare in Fryns syndrome. Therefore, the diagnosis of PKS should be considered whenever diaphragmatic hernia and short limbs are detected; however, in such cases the detection of the typical profile ma significantly contribute to establishing a diagnosis. In our case, the ultrasound scan, performed at 13 weeks, revealed this suggestive facial dysmorphism.

In conclusion, PKS is a sporadic pathology accessible to the prenatal diagnosis. It is necessary to evoke it in case of associated suggestive abnormalities: diaphragmatic hernia, micromelia of a rhizomelic type and facial dysmorphism (long Philtrum). These abnormalities can be diagnosed during the first trimester and must be looked for in case of increased nuchal translucency.

ACKNOWLEDGMENTS:

We want to thank the foetopathology team of Pr Gaigi Soumaya (Center of Maternity and Neonatology of La Rabta, Tunis), the genetics team of Pr Chaabouni Habiba (Charles Nicole Hospital, Tunis), Dr Ben Ghachame Sami (Private Medical doctor specialist in gynecology and obstetrics in Beja), Dr Meddeb Mounira (Genetics laboratory, Tunis)

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