PRENATAL DIAGNOSIS OF PATERNAL UNIPARENTAL ISODISOMY OF CHROMOSOME 14 (patiUPD14) WITH CHROMOSOMAL MICRO-ARRAY IN A FETUS WITH MULTIPLE CONGENITAL ABNORMALITIES

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CASE REPORT

The patient, a 43 years old primigravida woman, was referred at 12 weeks of gestation for prenatal diagnosis because of an increased nuchal translucency at ultrasound (3.8 mm, CRL 59 mm). The karyotype on uncultured chorionic villi was normal: 46,XX (15 cells, RHG banding). There were no particularities in the familial history nor consanguinity.
Chromosomal Micro-Array Analysis (CMA) was performed with PrecytoNEM (derived from Agilent 60K, resolution 400 Kb) and didn't show any unbalanced abnormality.
At 23 WG, a subsequent ultrasound showed multiple abnormalities : polyhydramnios, generalized oedema, dysmorphic features with long filtrum, small rounded ears, prefrontal oedema, very short femur length (<1° percentile) in contrast with the body weight estimated at the 83° percentile, abdominal wall eventration and large feet with abnormal hallux implantation (**Figure 1**).
Amniocentesis was performed to exclude a tetrasomy 12p (Pallister-Killian syndrome) possibly undiagnosed on chorionic villi because of a chromosomal feto-placental discrepancy: the karyotype was again normal and the Fish analysis ruled out tetrasomy 12p.
The parents opted for termination of pregnancy after counselling about the poor prognosis of the fetal malformations . Post-mortem examination evoked patUPD(14) (**Figure 2**)

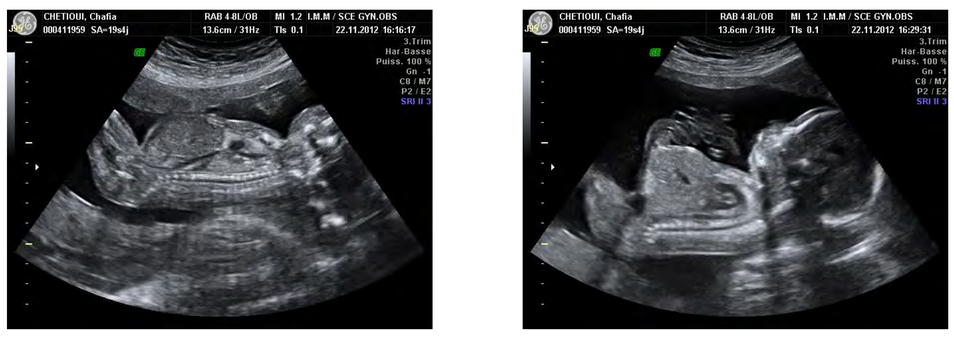

Figure 1 : Ultrasound at 23 weeks of gestation

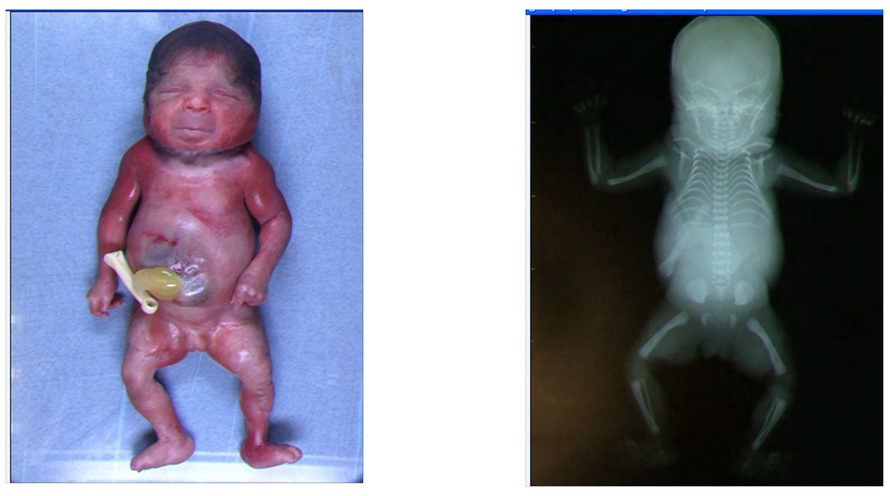

Figure 2 : Post-mortem examination
Left : Short limbs , contractures, diastasis recti, short thorax, dysmorphy
Right : X-ray showing "coat-hanger" ribs and platyspondyly

An additional CMA with Affymetrix CytoScan HD (SNP-array) on the amniotic fluid again did not show any pathogenic CNV but exhibited a complete isodisomy for chromosome 14 (**Figure 3**) .Paternal iUPD14 was confirmed by parental microsatellite segregation.
Parental karyotypes were normal.

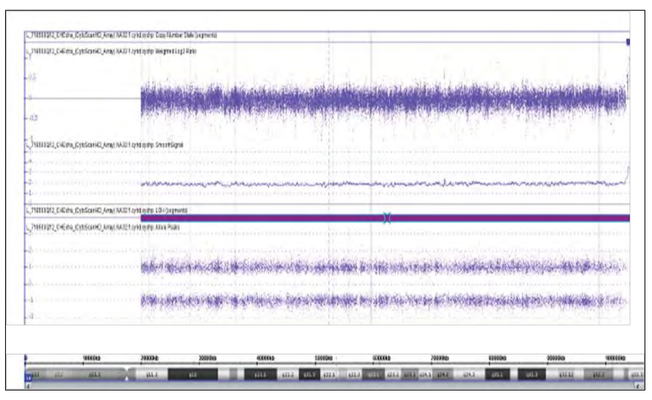

Figure 3 : **Cytoscan HD profiles of chromosome 14**
Top : Log2R = 2 , normal copy number
Bottom : allele difference plot showing complete uniparental isodisomy

DISCUSSION

The phenotype of neonatal patUPD14 -like syndrome is now well known: polyhydramnios, pathognomonic short "coat-hanger" thorax, dysmorphic features, diastasis recti, developmental delay and poor prognosis which explains the high frequency in spontaneous miscarriages: 1/81.
Prenatal features are less evident. Twenty four neonatal cases have been reported (**Table 1**): among prenatal findings , polyhydramnios was present in 22/24, atypical omphalocele in 4/24 , short thorax in 8/24, and "coat-hanger " ribs was prenatally demonstrated only in the two more recent cases. In about half of the cases, karyotype was abnormal with balanced robertsonian translocations involving one chromosome 14 and , in one case, a mosaïc supernumerary marker chromosome 14.

The relative frequency of the three **genetic mechanisms** that may cause the UPD (14) pat-like syndrome in patients with normal karyotype was recently studied in post-natal patients by Kagami : patUPD(14) is the more frequent (65.4%) followed by microdeletion involving the imprinted 14q32 region(19.2%) and epimutation of the imprinting centers (15.4%).
UPD(14) may result from different events, leading to heterodisomy (two homologs inherited from the same parent) or isodisomy (both homologs are identical) (**Table 2**).
Among the 17 patients with UPD (14)pat studied by Kagami, five were heterodisomic (trisomy rescue or gamete complementation) and twelve were isodisomic (monosomy rescue or post –fertilization mitotic error).

N of patients	Mattes (2006) 19	Yamanaka (2009) 4	Suzomori (2010) 1
Polyhydramnios	17	4	1
Thorax Small	3	4	1
Angled ribs	1	1 (Xrays33 WG)	1
"Coat-hanger"			1 (3D US 28WG)
Nuchal translucency or skin oedema	1	1	
Limbs Short	2	2	
Contractures	1	1	
Omphalocele or enlarged abdomen	1	3	
Malformations			
Pyelectasy	1	1	
Small stomach	1	1	
Others	1	2	
Dysmorphy			1 (3D US)
Abnormal Karyotype	9/18*	?	?

Table 1 : Prenatal findings of reported patients with UPD(14)pat
*** balanced robertsonian translocations/mosaïc supernumerary marker chromosome 14.**

GENETIC MECHANISM	SUBTYPE OF DISOMY
Trisomy rescue	Meiose I with CO : *Heterodisomy/Segmental Isodisomy* Meiose I without CO : *Heterodisomy* Meiose II with CO *: Heterodisomy/Segmental Isodisomy* Meiose II without CO : *Complete isodisomy*
Monosomy rescue	*Isodisomy*
Gametic complementation	Same subtypes than trisomy rescue (for the diploid gamete).
Post-fertilization mitotic error	*Isodisomy*

Table 2 : Genetic mechanisms for UPD(14)
CO : crossing-over

Single nucleotide polymorphism (SNP)-based microarray, in addition to copy-number variations diagnosis, provide information on genotype at multiple polymorphic loci, allowing the detection of homozygous regions or LCSH: long-continuous stretch of homozygosity. When LCSH is limited to one entire chromosome with normal Log2 ratio (neutral LOH), complete iso-UPD may be suspected and has to be confirmed by parental microsatellite segregation. However, heterodisomy may be missed and will only be suspected in the presence of large multiple LCSH, limited to one chromosome, spread among normal biallelic regions, depending on the occurrence and the size of crossing-over before the meiotic accident (**Figure 3**).
In addition, allele frequency data are helpful for the diagnosis of some residual trisomy ,above 30%, in case of trisomy rescue.
Nevertheless, prenatal use of SNP-based microarray must be cautious. Indeed, SNP-array may provide some incidental findings like consanguinity or uncertain results leading to confusing genetic counselling, for example when LCSH affect not imprinted chromosomal regions or regions encompassing some genes for autosomal recessive disorders.

Figure 3 : Cytoscan HD profiles suggesting uniparental heterodisomy
Allele plots data show large blocks of homozygosity (red squares)

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Laboratoire CERBA

http://www.lab-cerba.com/images/vous_informer/AB_ESHG_juin2013.pdf

CONCLUSION

PatUPD(14) is not very frequent but have a poor prognosis. The pathognomonic "coat-hanger" sign must be searched in every pregnant women with unexplained polyhydramnios.
When a prenatal SNP-microarray is performed, the allele plots data may be useful to suggest the diagnosis of patiUPD(14) and help the parents and the medical staff to manage the pregnancy.