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Risk estimation of uniparental disomy of chromosome 14 or 15 in a fetus with a parent carrying a non-homologous Robertsonian translocation.

Should we still perform prenatal diagnosis?

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ABSTRACT

Uniparental disomy (UPD) testing is currently recommended during pregnancy in fetuses carrying a balanced Robertsonian translocation (ROB) involving chromosome 14 or 15, both chromosomes containing imprinted genes. The overall risk that such a fetus presents a UPD has been previously estimated to be around ~0.6-0.8%. However, because UPD are rare events and this estimate has been calculated from a number of studies of limited size, we have reevaluated the risk of UPD in fetuses for whom one of the parents was known to carry a nonhomologous ROB (NHROB). We focused our multicentric study on NHROB involving chromosome 14 and/or 15. A total of 1747 UPD testing were performed in fetuses during pregnancy for the presence of UPD(14) and/or UPD(15). All fetuses were negative except one with a UPD(14) associated to a maternally inherited rob(13;14). Considering these data, the risk of UPD following prenatal diagnosis of an inherited ROB involving chromosome 14 and/or 15 could be estimated to be around 0.06%, far less than the previous estimation. Importantly, the risk of miscarriage following an invasive prenatal sampling is higher than the risk of UPD. Therefore, we do not recommend prenatal testing for UPD(15)mat, UPD(14)mat, UPD(14)pat for these pregnancies and parents should be reassured. Sonographic examination will help detecting the extremely rare fetuses with Prader-Willi, Kagami-Ogata or Temple syndrome. Given the fact that no sonographic features can reliably detect fetuses with Angelman syndrome, a prenatal invasive sampling to test UPD(15)pat could be discussed with future parents.

Keywords:

Uniparental disomy (UPD), UPD of chromosome 14 and 15, UPD(14), UPD(15), Inherited Robertsonian Translocation, Trisomy rescue, monosomy rescue, Gametic complementation

Introduction

Uniparental disomy (UPD) occurs when both copies of a chromosome, or part of a chromosome, are derived from a single parent. UPD is called heterodisomy when a pair of non-identical chromosomes is inherited from one parent or isodisomy when a single chromosome from one parent is duplicated. UPD may have clinical relevance for several reasons. Isodisomy leads to large blocks of homozygosity, which may lead to the uncovering of recessive alleles. Either isodisomy or heterodisomy can disrupt parent-specific imprinted genes, resulting in imprinting disorders, among them the well-known Prader-Willi (PWS; OMIM 176270) and Angelman (AS; OMIM 105830) syndromes for chromosome 15. PWS is characterized by short stature, obesity, hypogonadism, and learning difficulty. Approximately 70% of individuals with PWS carry a microdeletion at 15q11q13 of the paternally derived homolog. Most (25 %) of the remaining patients with PWS have maternal UPD(15). AS is characterized by severe learning difficulties, epilepsy and ataxic gait. Approximately 70% of individuals with AS carry an interstitial microdeletion of the same 15q11q13 region as in PWS, but in this case on the maternally derived homolog. About 2% of the remaining patients present paternal UPD(15).

Three different mechanisms explain UPD: (i) trisomy rescue (ii) monosomy rescue and (iii) gametic complementation [1]. However, the main mechanism responsible for UPD is trisomy rescue mostly related to advanced maternal age [2]. This is highlighted by the higher proportion of maternal UPD to the etiology of PWS compared to that of paternal UPD to the etiology of AS (25% versus 2%). Apart advanced maternal age, any condition predisposing to aneuploid gametes increases the risk for UPD. Therefore, individuals carrying a balanced Robertsonian translocation (ROB) have an increased risk of aneuploid embryos, miscarriages and UPD following trisomy rescue.

UPD testing is currently recommended in fetuses carrying a balanced ROB involving chromosome 14 or 15 [1]. Thus, most of the cytogenetic laboratories follow this recommendation and some of them attempted to estimate the risk of UPD following prenatal diagnosis of a ROB involving chromosome 14 or 15 [3,4,5,6,7,8]. From these combined data, the overall risk that a fetus with a non-homologous ROB (NHROB) presents a UPD has been estimated to be around ~0.6-0.8% [9]. However, because UPD are rare events and this estimate has been calculated from a number of studies of limited size, we have reevaluated the risk of UPD in fetuses for whom one of the parents was known to carry a NHROB. We focused our multicentric study on NHROB involving chromosome 14 and/or 15, the two chromosomes containing imprinted genes involved in ROB.

Patients and Methods

Data were collected from 28 French genetic laboratories, all members of the “Association des Cytogénéticiens de Langue Française (ACLF; the French-Speaking Cytogeneticists Association)” and/or the Association Nationale des Praticiens en Génétique Moléculaire (ANPGM; National Association of Molecular Genetics Practitioners). The current study was set up to gather the results of UPD survey, over more than 10 years, in prenatal period. The study followed the local ethical guidelines of CHU Nantes, France. The study was reviewed and approved by the Board of the ACLF.

The genetic laboratories provided the results of UPD(14) and UPD(15) testing in fetuses for whom one of the parents was known to carry a NHROB. Fetal karyotype was obtained from amniotic fluid and/or chorionic villi samples. Eight laboratories also provided the results of UPD testing performed in fetuses with normal karyotype but conceived by a parent carrying a NHROB.

UPD tests were performed using different methods depending on the chromosome involved. UPD(15) tests were carried out using MS-MLPA Probemix (ME028, Prader-Willi/Angelman) from MRC Holland according to the manufacturer's protocol or using custom sets of microsatellite genetic markers (short tandem repeats). UPD(14) tests were performed using the Epitect bisulfite kit Qiagen ® enabling the study of the methylation status of MEG3 (Maternally Expressed Gene) on chromosomal region 14q32.2 followed by confirmation with microsatellite genetic markers on chromosome 14 for positive cases.

Results

Twenty-eight genetic laboratories participated to this retrospective study. A total of 1747 UPD diagnoses were performed.

We obtained additional data for 832 fetuses among them 661 inherited the balanced NHROB while 171 had a normal karyotype. Thus, the chromosomes involved in the translocation were obtained for 661 fetuses as well as the sex of its carrier parent (table 1). No significant difference was observed in the sex of the carrier parent (336 translocations were present in the father and 325 in the mother). As expected, the most frequent translocation was the rob(13;14) (394 fetuses among 661) followed by the rob(14;21) (112 fetuses among 661). The other translocations (i.e. rob(14;15) rob(14;22), rob(13;15), rob(15;21) and rob(15;22)) were observed in the remaining 115 fetuses.

Table 1: Type of Robertsonian translocation and parental origin

| Fetal NHROB | Paternal | Maternal |
|-------------|----------|----------|
| rob(13;14) | 205 | 189 |
| rob(14;15) | 35 | 17 |
| rob(14;21) | 54 | 58 |
| rob(14;22) | 7 | 21 |
| rob(13;15) | 18 | 13 |
| rob(15;21) | 8 | 11 |
| rob(15;22) | 9 | 16 |
| Total | 336 | 325 |

Among the 1747 fetuses diagnosed for UPD, 686 were tested for UPD(15) and 1061 for UPD(14). No fetuses showed UPD(15). Only one fetus out of 1061 showed UPD(14) of maternal origin. The fetal karyotype was 45,XX,rob(13;14)(q10;q10) and the translocation was inherited from her 28-year-old mother. Intrauterine growth retardation was noted during pregnancy. After genetic counseling the parents decided to continue the pregnancy. A girl was born at 40 weeks of gestation. Birth parameters were less than 10th percentile (weight 2965 g and length 46 cm). The child was not available for postnatal follow up.

Among the 171 fetuses with normal karyotype but conceived by a ROB carrier parent, none of them showed UPD for chromosome 14 or 15.

Discussion

The concept of UPD was first introduced by Eric Engel in 1980 when he hypothesized that patients might present a genetic disorder caused by the presence of two copies of the same homolog inherited from only one of their parents [10]. As explained in his memories, his paper “slept on a shelf for several years waiting for more evolution in molecular techniques to be able to study the parental origin of chromosomes from their DNA polymorphisms” [11,12] Warburton D. 1988 *AJHG* 1988;42:215-216). Finally, proof of concept was achieved after publication of a patient with cystic fibrosis [13]. Only one of his parents was carrying a heterozygous pathogenic variant in the *CFTR* gene, the patient carried the variant in a homozygous state resulting from an isodisomy of chromosome 7 of maternal origin. Afterwards, during the late 1980s and early 1990s, the first patients with PWS and AS caused by maternal and

paternal UPD(15), respectively, and patients with Temple Syndrome (OMIM 616222) and Kagami-Ogata syndrome (OMIM 608149) caused by maternal and paternal UPD(14), respectively, were reported [14,15]. For those cases, the UPD was suspected since the patient was a carrier of a balanced ROB involving either chromosome 15 or 14 inherited from a healthy carrier parent.

After these first descriptions, several teams reported patients with UPD(14) or UPD(15) [16,17,18,19] likely corresponding to the unsolved cases left in drawers for a very long time. Overall, thirty years after proof of concept of UPD, very few cases of UPD(14) and UPD(15) associated to an inherited NHROB involving chromosome 14 or 15 have been reported. Among more than 600 cases of UPD(14) and UPD(15) registered in a regularly updated database, only 31 cases are associated to a NHROB, of which 20 cases are *de novo* and 11 are inherited (Pr. Thomas Liehr, Jena lab-Germany <http://upd-tl.com/upd.html> and [20]. Of note, these combined data suggest that the risk of UPD is significantly higher when the translocation is *de novo* in the fetus than when it is inherited from a carrier parent (twice more frequent). Most of these patients are case reports and cannot be used to estimate the risk of UPD for a fetus conceived by a ROB carrier (table 2).

Table 2: Studies estimating the number of fetuses with UPD and an inherited or a *de novo* NHROB

| Series | Nbr fetus | Nbr of UPD cases associated to an inherited ROB | Nbr of UPD cases associated to a <i>de novo</i> ROB |
|-----------------------|-----------|--|---|
| Sensi A. (2004) | 160 | One case of UPD(14)mat, rob(14;22)mat | |
| Silverstein S. (2002) | 42 | | one case of upd(14)mat, rob(13;14)dn |
| Ruggeri A. (2004) | 83 | | one case of upd(14)mat, rob(14;21)dn |
| Jay AM. (2001) | 22 | | |
| Barton DE. (1996) | 14 | | one case of upd(14)mat, rob(13;14)dn |
| Kotzot D. (2000) | 458 | | Six cases of UPD |
| | 779 | One case of UPD associated to an inherited ROB (0.13%) | 9 cases of UPD (UPD risk 1.16%) |

In 2006, Lisa G. Shaffer combined the published data and estimated the risk of UPD when a balanced NHROB (de novo or inherited) is detected in a fetus to be around 0.6-0.8% (3 fetuses with UPD among 477 fetuses studied). Two UPD were identified in fetuses carrying a *de novo* ROB while one fetus inherited the balanced ROB from a parent. Therefore, the estimated risk of UPD associated to an inherited ROB is approximately 0.2% (1/477 fetuses). This risk is likely overestimated since only one negative cohort was included, other negative cohorts might have been unpublished [6]. In our ten years retrospective study involving 28 genetic diagnostic laboratories, >1500 fetuses carrying a ROB inherited from a healthy parent were tested during pregnancy for the presence of UPD(14) and/or UPD(15). All fetuses were negative except one with a UPD(14)mat associated to an inherited rob(13;14). The risk of UPD following prenatal diagnosis of an inherited ROB involving chromosome 14 and/or 15 could be estimated around 0.06%, far less than the previously estimation of 0.6%. Importantly, this estimated risk of 0.06% is less than the risk of miscarriage following invasive fetal sampling, despite the fact that this estimated risk of miscarriage is still controversial (reevaluated by Akolekar R. (2015)[21]. Until recently, when a parent was carrying a ROB involving chromosomes 13 or 21, an invasive fetal sampling was discussed to exclude a trisomy 13 or 21. If the ROB involved chromosomes 14 or 15, UPD testing was performed at the same time as karyotyping. Currently, non-invasive prenatal diagnosis (NIPT) is replacing this invasive procedure. Therefore, the only purpose of an invasive procedure would be UPD testing.

UPD following monosomy rescue are rarely observed probably because the embryo does not survive enough to duplicate the autosome and become isodisomic [9]. To the best of our knowledge, only two patients conceived by a ROB carrier were reported postnatally with UPD following monosomy rescue. Recently, Bramswig NC et al. reported a patient with AS caused by UPD(15) and a normal karyotype. The two paternal chromosomes 15 were inherited from his healthy father. The mother was a carrier of a balanced rob(14;15) [22]. The second patient is a girl presenting with polyhydramnios, short limbs and small thorax during pregnancy [23]. After delivery, a UPD(14)pat was diagnosed explaining the clinical features in this child with a normal karyotype (46,XX). Familial study showed that her mother is carrier of a rob(13;14). In most laboratories participating in the present study, diagnosis of UPD was carried out if a balanced ROB was detected in the fetus. However, in eight laboratories, all pregnancies conceived with one of the parents carrier of a balanced ROB were tested for UPD regardless of fetal karyotype (carrying the balanced ROB or not). No UPD(14) or UPD(15) was detected in 171 fetuses with normal karyotype which is in agreement with the rare risk of UPD following monosomy rescue. [5] also studied 18 fetuses with a normal karyotype but conceived by a parent carrying a ROB to

evaluate the risk of monosomy rescue and did not identify any UPD. These results confirm that UPD following a monosomy rescue is extremely rare.

Another mechanism leading to UPD is gametic complementation. This mechanism is extremely rare and not easy to prove unless there is a structural chromosomal anomaly. Up to now, two cases of gametic complementation have been well documented. Cotter PD et al (1997) [24] reported a patient presenting with Kagami-Ogata syndrome (OMIM 608149) due to a UPD(14)pat. The parents of the patient were carriers of two different Robertsonian translocations, the mother with rob(14;21) and the father with rob(13;14). These two parental translocations favor the fertilization of a nullisomic gamete for chromosome 14 with a disomic one. Such observation was also observed in another case of Kagami-Ogata syndrome with parents both carriers of chromosomal translocations: the father with rob(13;14) and mother carrier of a reciprocal translocation t(1;14)(q32;q32) [25]. When both parents carry a chromosomal translocation involving chromosomes 14 and/or 15, the risk of UPD is highly increased and a prenatal UPD test should be considered.

Our data show that the risk of UPD following prenatal diagnosis in a fetus who inherited ROB involving chromosome 14 and/or 15 is very low. Therefore, if prenatal UPD testing is not done, what is the risk of misdiagnosis of fetal UPD(14) or UPD(15)? During pregnancy, most fetuses with Prader-Willi, Kagami-Ogata or Temple syndrome present abnormal features which can be detected by ultrasound examination. Gross N et al (2015) [26] performed a retrospective study on the prenatal ultrasound records of 106 patients with PWS diagnosed postnatally. In this study, the following ultrasound features were studied: small for gestational age (SGA, ≤ 10 centile), asymmetrical intrauterine growth, polyhydramnios and breech position. The authors showed that 98% of the fetuses with PWS presented at least one of these ultrasound features during pregnancy.

In postnatal, patients with Kagami-Ogata syndrome (OMIM 608149) present with feeding difficulties, development delay, intellectual disability and skeletal abnormalities especially a bell-shape thorax and increased coat-hanger angle. In a review, UPD(14)pat was detected in 23/34 patients showing that UPD is a common mechanism leading to the syndrome. In prenatal period, ultrasound signs are almost always observed. The most common fetal ultrasound signs are particular thorax abnormalities small bell-shaped thorax and an abnormal coat-hanger appearance observed in all cases. Polyhydramnios, requiring one or more amnioreduction, is also reported in all cases. In more than 80% of fetuses, a placentomegaly could also be detected [27]. The association of these signs is considered a hallmark for UPD(14)pat in prenatal period.

Thirty-two patients with Temple Syndrome (TS14, OMIM 616222) have been reported [28]. The main features in postnatal period are growth failure, hypotonia, small hands and feet, precocious puberty. Intellectual disability is not frequent. UPD is also a common mechanism leading to the syndrome since 23/32 patients presented with UPD(14)mat. In prenatal period, 90% of the fetuses present an IUGR (a mean of -2.2 SD). A hypoplastic placenta can also be observed.

Taken together, these data show that at least one abnormal sonographic feature is detected in the majority of the fetuses with Prader-Willi, Kagami-Ogata or Temple syndrome [26,27,28 and table 3]. In the context where a parent is a carrier of a ROB involving chromosome 14 or 15, the detection during pregnancy of a single abnormal ultrasound finding should lead to a prenatal testing for UPD.

Table 3: Prenatal features in fetuses with UPD(14) or UPD(15)

| UPD | dup(14)pat Kagami Syndrome | dup(14)mat Temple syndrome | dup(15)mat Prader Willi Syndrome | dup(15)pat Angelman Syndrome |
|-------------------------------|---|-------------------------------|---|---------------------------------|
| Ultrasonographic signs | Small bell-shaped thorax with coat-hanger appearance of the ribs and Polyhydramnios (all cases) | RCIU (Almost all cases 97%) | Polyhydramnios, Decreased fetal movement Breech presentation Mild prenatal growth retardation 2% of cases present no ultrasonographic sign | No ultrasonographic sign |

Regarding AS, which can be caused by UPD(15)pat, there are no ultrasound features in an affected fetus which could reliably lead to a suspicion of this syndrome and a prenatal diagnosis. Therefore, a prenatal testing for UPD(15)pat could be proposed (Clinical and genetic aspects of Angelman syndrome, [29]). Nevertheless, to the best of our knowledge, no patients with AS associated to a UPD, diagnosed following a prenatal testing triggered by a parental ROB involving chromosome 15, have been reported. Likewise, no UPD(15)pat has been detected in our series of 686 tests.

In conclusion, we estimate the risk of UPD when a parent is carrier of a NHROB involving chromosome 14 and/or 15 to be about 0.06%, ten times less than the previously published estimation. The risk of miscarriage following an invasive prenatal sampling is higher than the risk of UPD. Therefore, we do not recommend prenatal testing for UPD(15)mat, UPD(14)mat, UPD(14)pat in this context and parent should be reassured. Sonographic examination will help detecting the extremely rare fetuses with Prader-Willi, Kagami-Ogata or Temple syndrome. Given the very low risk of UPD following malsegregation/rescue, a prenatal

invasive sampling to test UPD(15)pat responsible for Angelman Syndrome could however be discussed with future parents.

Consent

Written informed consent was obtained from the parents.

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