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Comparison of perinatal factors in deletion versus uniparental disomy in Prader-Willi syndrome

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Abstract

INTRODUCTION—Prader-Willi syndrome (PWS) is caused by a deficiency of imprinted genes in the 15q11-q13 region and is characterized by prenatal-onset of hypotonia, poor feeding, childhood-onset obesity, hyperphagia, short stature, facial dysmorphism, intellectual disability, and behavioral problems. We studied perinatal factors in a cohort of 64 people with PWS resulting from paternal deletion of 15q11-q13 and maternal uniparental disomy for chromosome 15 (UPD).

METHODS—We recruited 34 individuals with deletion and 30 with UPD. We compared the frequency of multiple prenatal and neonatal factors with the general population as well as between the two genetic subtypes.

RESULTS—Of the 64 individuals with PWS, fetal movements were decreased in 82.8%, 31.7% were born prematurely, 42.1% by Cesarean section, and 35.9% required oxytocin induction, Apgar scores were low in 34.6%, 96.8% had feeding difficulty, 50% needed tube feeding, and 6.2% subsequently had gastrostomy tube placement. On comparing findings in the deletion versus the UPD groups, we did not find many significant differences. We however found a higher maternal age, and also later age at diagnosis in the UPD versus the deletion group.

CONCLUSION—PWS subjects have higher rates of perinatal complications, especially Cesarean section rate, hypotonia, and low Apgar scores compared to the general population. We did not find many differences between the genetic subtypes, except for later age of diagnosis of the UPD 15 group suggesting a milder phenotype. We also found that the mothers in the UPD were older, supporting the hypothesis that UPD results from non-disjunction associated trisomy rescue.

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INTRODUCTION

PWS is a complex genetic disorder characterized by prenatal onset of hypotonia, infantile poor feeding and growth, hyperphagia with subsequent obesity, short stature, typical facial dysmorphism, psychomotor delay, behavioural abnormalities, and cognitive impairment. Deficiency of imprinted genes from the paternal 15q11-q13 is the cause of this neurodevelopmental disorder. The maternal copy of several genes in this region is typically inactive due to methylation, this parent of origin effect on gene expression being called genetic (or genomic) imprinting. PWS has three different molecular causes: a) deletion of the paternal copy of 15q11–13, present in approximately 70% of those with PWS, b) maternal uniparental disomy (UPD) for chromosome 15, in which both copies of chromosome 15 are maternally inherited with no paternally inherited region of chromosome 15, accounting for approximately 28% of cases of PWS, and c) imprinting center defects accounting for 1–2% of those diagnosed with PWS [Driscoll et al.1998]. Differences between the frequencies of some clinical features have been identified between those with deletion and those with UPD as a cause of their PWS, though no feature is caused exclusively by only one of the genotypes [Driscoll et al.1998].

This study aimed to characterize the perinatal complications in a cohort of individuals with PWS and compare findings in the two most common genetic types: deletion and UPD. We review the literature on perinatal complications in PWS (Fong & De Vries, 2003) and also compared our findings with larger previous studies in France (Dudley & Muscatelli, 2007), (Bar et al., 2017), and the United Kingdom [Whittington et al. 2008]

METHODS

This research is part of a project started at Case Western Reserve University and continued at the University of California, Irvine. Institutional review board approval was obtained from University of California, Irvine for this study. Informed consent was obtained from the parents and assent from the patient if aged above 7 y. Affected subjects aged 3 y. to adulthood of both sexes were included in the study with no control population. Individuals needed confirmation of the diagnosis of PWS by molecular testing and were excluded if they only had a clinical diagnosis of PWS. Subjects were recruited either during patients visits, by letter or by telephone by the project coordinator. Subjects were assessed over three days for multiple historical and clinical parameters, including detailed history of the pregnancy, labor and delivery as obtained from parental report and available record review. The objective of this study was to collect a cohort with approximately equal numbers of individuals with PWS due to deletion and due to UPD, with the aim of studying phenotypic differences between the two genotype groups. The current project looked to assess the early manifestations, including pregnancy, delivery and early neonatal manifestations and compare it to the USA population data and between genotype groups. We reviewed perinatal clinical features including decreased fetal movements, polyhydramnios, malpresentation, and assisted vaginal deliveries with forceps or vacuum or invasive Cesarean section as well as neonatal features including birth weight, length, head circumference, Apgar scores, hypotonia, feeding difficulties, frequency of gavage feeding, and gastrostomy tube placement.

ANALYSIS

The data was analysed using the JMP statistical package. Contingency tables were generated. Parametric variables were expressed as mean (±SD) while non parametric variables were expressed as median and range. Categorical variables were expressed as frequencies in each group. Student t -test was used to compare means. Non parametric variables were compared using Mann-Whitney U. Chi-square and Fisher exact test were used for categorical variables. All tests were 2-tailed with statistical significance considered at $p < 0.05$.

RESULTS

Sixty-four patients participated in this study including 34 patients with deletions and 30 patients with maternal UPD; this cohort including 34 males, (18 with deletion and 16 with UPD) and 30 females (16 with deletion and 14 with UPD). The mean age of diagnosis in the overall group was (4.9 y.) It was significantly later in the UPD group (5.8 y.) versus the deletion group (4.3 y.).

Data resulting from this study are summarized in Table 1. Maternal age was significantly higher in the UPD group (36.7± 4.3 y.) versus the deletion group (28.7 ± 3.5 y.) ($p = 0.0001$). Fetal movements were reported as subjectively decreased in 53 subjects (82.8%). Only 8 mothers reported normal fetal movements, and these were equally distributed between the deletion and UPD groups. No statistical significance was found between the groups for timing of the delivery or birth weight in this study.

There was no statistically significant difference found between the UPD and deletion groups for incidence of Cesarean versus vaginal delivery. No statistical difference for the number of subjects having either a premature or post 42 week delivery between the genetic groups was noted ($p = 0.75$). The difference in the mean birth weight for those with deletion (n=29) was 2.90 ± 0.61 kg and for UPD (n=29) was 2.86 kg ± 0.5), these differences not being significant ($p=0.8$), but there is high incidence of low birth weight at 18% versus 8% in United states in 2015 CDC report (Martin et al., 2017).

Of the 63 patients with perinatal information, 20 (31.7%) were born prematurely prior to 37 weeks (11 deletion/ 9 had UPD),which is much higher prematurity rate of 9.6% for all the deliveries in United States in 2015 as reported by CDC (Martin et al., 2017), 23 were born at term (38 to 42 weeks) (11 deletion/12 UPD) and 20 were post term (>42 weeks) (10 deletion/ 10 UPD). Among the 27 who had a Caesarean section (42.1%) 16 had deletion and 11 had UPD. Among the 35 who had a vaginal delivery (54.4%), 23 requiring oxytocin induction (35.9%) (10 deletion/13 UPD) and only 12 (18.7%) had a normal spontaneous vaginal birth (7 deletion/5 UPD). The entire cohort (96.8%) except for two individuals had feeding problems at birth: 50% needed gavage feeding of whom four patients (6.2%) needed invasive gastrostomy tube placement. Comparison with prior studies of perinatal problems in PWS was also performed (Table 2).

We also categorized our PWS subjects into two groups based on the year of birth: Group 1 included patients born prior to 1992 and Group 2 subsequent to 1992 when DNA testing by

methylation studies was available. The mean age of diagnosis for the group born after 1992 was (3.4 y.± 0.9 y.) with a range from one month to 13 y., while the mean age of diagnosis for the group born before 1992 was (4.8 y.± 1.4 y.) with a range from one month to 26 y. The difference is statistically insignificant (Mann–Whitney U-test; P= 0.68).

DISCUSSION

Prader–Willi syndrome (PWS) is a complex neurobehavioral disorder that was first described in 1956 by Prader, Labhart and Willi (Prader, Labhart, & Willi, 1956). The clinical diagnosis of PWS is challenging, being based on a constellation of non-specific clinical features that change over time (Trifiro et al., 2003). Subtle diagnostic features that evolve over time and inappropriate choice of the initial molecular test have led to delayed diagnosis in earlier publications. The past few decades have witnessed diagnosis at earlier age due to increase in the availability of molecular diagnostic tests and improved awareness of PWS features (Bar et al., 2017), (Lionti, Reid, White, & Rowell, 2015). Interestingly however, the age of diagnosis continues to be delayed in some of the contemporary studies (Dobrescu, Chirita-Emandi, Andreescu, Farcas, & Puiu, 2016). This has driven a research interest in the perinatal features of PWS since early diagnosis and adequate management are crucial to prevent obesity and its medical consequences, and improve cognitive skills (Bar et al., 2017). Butler 2017 (Butler, 2017) reported that fetal growth restriction, and decreased fetal movements are the most common perinatal features. Gross et al.(2015)(Gross, Rabinowitz, Gross-Tsur, Hirsch, & Eldar-Geva, 2015) confirmed similar findings on reviewing the obstetric records of 106 individuals with PWS compared to the general population. They recommended the use of DNA methylation test for prenatal genetic screening whenever combination of polyhydramnios and small for gestational age (Gross et al., 2015). Decreased fetal movements were added as one of the minor diagnostic criteria by Holm et al. (1993) (Holm et al., 1993). Decreased fetal movements were also seen in 85.6% of our study population which is similar to previous reports.

Although this study may have been affected by recall bias, there is clearly a high rate of pregnancy and delivery complications in babies with PWS. There is a significantly higher rate of Cesarean sections and induced labor compared with general population in the USA, regardless of the genetic etiology of the PWS.

Comparison with prior studies of perinatal problems in PWS is shown in Table 2. Dudley et al. (2007) found a significantly high rate of induced labor, prematurity, and Cesarean section and also found significantly higher rates of prematurity, induced labor and advanced maternal age in a UPD group relative to a deletion group (Dudley & Muscatelli, 2007). In our cohort, similar high rates of Cesarean section (42.1%), hypotonia (93.4%) and prematurity (31.7%) were observed but we did not find any statistically significant difference in subgroup analysis except for the advanced maternal age in the UPD group versus the deletion group. In concordance with our results,Whittington et al. (2008) did not find any significant differences between deletion and UPD groups in the above mentioned factors, including feeding difficulty. In contrast there were statistically significant differences for the mother's age at delivery and birth weight between both groups. UPD was positively correlated and deletion was negatively correlated with the two factors

(Whittington, Butler, & Holland, 2008). Bar et al. (2017) found also significantly higher maternal age in UPD group in comparison with non UPD. Our study found higher rate of prematurity , decreased fetal movements, and feeding difficulty (31.7%, 85.6%, 96.8%) respectively in comparison with the French study (20%, 27%, 84.4%) respectively (Bar et al., 2017).

The introduction of new molecular testing has permitted easy confirmatory diagnosis of 100% of PWS patients. Several studies report a very early age at diagnosis compared to our study. Bar et al. (2017) reported that the earliest median age of diagnosis in France is 18 days (Bar et al., 2017), with other studies reporting a mean age at diagnosis of one month, range (0.51– 4.98 months) (Smith et al., 2003), and 6.5 months with range from one week to 8 y. (Vogels & Fryns, 2004). Our study in contrast found a mean age of diagnosis of (4.9 y. ± 5 y.) with range from one month to 26 y. If and when newborn screening for PWS is available, all genotypes will be picked up very early and early management and treatment will be available for all individuals with PWS. We also found that the age of diagnosis was significantly delayed in the UPD group to 5.8 y. ±1 y. These findings were reported by several other researchers including Gunay-Aygun et al. (1997) (Gunay-Aygun, Heeger, Schwartz, & Cassidy, 1997), Dykens et al. (2002) (Dykens, 2002),Hartley et al. (2005) (Hartley, Maclean, Butler, Zarcone, & Thompson, 2005) and Cassidy et al. (2012) (Cassidy, Schwartz, Miller, & Driscoll, 2012). This has be attributed to a milder phenotype with less typical facial features, milder behavioral problems, and higher verbal intelligence quotient in the UPD group leading to later diagnosis. In contrast, however, Dobrescu et al (2016) reported that individuals with non-deletion PWS were diagnosed at a relatively younger age comparison to those with deletions (6.7 y. ± 4.6 y. versus 8.11 y. ± 5.6 y. respectively) (Dobrescu et al., 2016).

Imprinted genes are increasingly thought to play a large part in fetal growth and development. This study adds supportive data to this theory as there are pre-delivery manifestations. This data supports the previously reported studies suggesting that there is severe disturbance in growth and neurodevelopment that starts in early fetal life (Dudley & Muscatelli, 2007).

The repeat Cesarean rate in the US is over 90% and it is not known from our data collection if any of the Cesarean in our patients were because of a previous Cesarean. The USA rates of Cesarean have been rising over the last decade. Many of the individuals in the current study were born prior to 2000, the year of birth ranging from 1963–1999. The overall rate of Cesarean has increased by 40% since 1996, an increase in the primary rate from 14.6% to 20.6%. By 2004 this rate had increased to 29.1% according to the Division of Vital Statistics of the CDC. As all of the participants in our study were born before 1999, even at a conservative estimate of the USA rate of 20–25% the rate of Cesarean in the PWS group we studied is almost double the US population rate (Center for disease control and prevention, 1981–2003; 1981).

CONCLUSIONS

Our study highlights some of the perinatal complications of PWS in a cohort of US patients. These complications include hypotonia, decreased fetal movements, high Cesarean rate, induced labor, assisted vaginal delivery, prematurity, and feeding difficulties. The cause of these perinatal difficulties is not known, but may relate to the profound hypotonia that is universal in PWS. The perinatal problems might play a role in the development of characteristic early postnatal difficulties (lethargy, poor suck) and subsequent developmental manifestations. Further prospective natural history studies may help to answer these questions. Our study also demonstrates later age of diagnosis in the UPD group in comparison with the deletion group, which may be due to less typical clinical phenotype and highlights the need for implementing PWS screening to be part of any newborn screening program. We hope that better understanding of the perinatal features of PWS could help in early diagnosis and prevention of associated comorbidities.

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Table1

Comparison of perinatal factors in deletion versus uniparental disomy in Prader-Willi syndrome

	Total= 64	Deletion (N=34)	UPD (N=30)	p-value
Gender				
Male	34 (53.1%)	18 (52.9%)	16 (47%)	0.814
Female	30 (46.8%)	16 (53%)	14 (46%)	
Gestational age(N=63)				
Preterm <37 wks.	20 (31.7%)	11 (32%)	9 (30%)	0.750
Full term	23 (36.5%)	11 (32%)	12 (40)	
Postdates >42wks	20 (31.7%)	10 (29.4%)	10 (33.3%)	
Mean maternal age ± SD (y.)	30 ± 4.7	28.7 ± 3.5	36.7 ± 4.3	<0.001
Mean birth weight ± SD (grams)	2882 ± 0.56	2900 ± 0.61	2860 ± 0.50	0.811
Mean birth length ± SD (cms.)	49.5 ± 5.3	50.5 ± 2.7	48.4 ± 7.1	0.125
Gastrostomy	4 (6.2%)	1 (2.9%)	3 (10%)	0.270
Gavage feeding	32 (50%)	18 (52.9%)	16 (53.35)	0.821
Feeding problems after birth	62 (96.8%)	32 (94.1%)	30 (100%)	0.322
Cesarean section	27/64 (42.1%)	16/34 (47%)	11/30 (36.6%)	0.417
Hypotonia	54 (84.3%)	26 (76.4%)	28 (93.3%)	0.081
Age of diagnosis(y.)	4.9 ± 5	4.3	5.8	0.017
Mean age of onset of hyperphagia ±SD (y.)	2.7 ± 1.2	2.5 ± 0.75	2.9 ± 2	0.215
Mean one minute Apgar score ±SD	5.9 ± 2.3	6.7 ± 2	5.5 ± 2.4	0.374
Low Apgar Scores (<7) at one minute	(60.7%)	(35.3%)	(64.7%)	0.442
Mean 5 minute Apgar score ±SD	7.8 ± 1.1	7.7 ± 1	8 ± 1.2	0.882
Low Apgar Scores (<7) at five minutes	(34.6%)	(44.4%)	(55.6%)	0.189

Table 2

Comparison with prior studies of perinatal problems in PWS

	US (N=64)	UK (N=46) [Whittington Butler and Holland 2008]	France (N=86) [Dudley and Muscatelli 2007]	France (N=61) [Bar et al 2017]
Decreased fetal movements	53 (85.6%)	(67.4%)	(47.6%)	(27%)
Preterm ≤ 37 wks.	20 (31.7%)	(37%)	(15%)	(20%)
Induction	23 (35.9%)	(37%)	(60.4%))	NA
Vaginal delivery	35 (56.5%)	(17.4%)	(41.8%)	(32.7%)
Caesarean Section	27 (42.1%)	(52.2%)	(53.4%)	(67%)
Hypotonia	54 (84.3%)	(100%)	(96.5%)	(76.1%)
Feeding difficulty	62 (96.8%)	(100%)	(82.5%)	(84.4%)
Mean maternal age				
Deletion	28.7	31.4	29.3	31
UPD	36.7	37.9		38
Mean one minute Apgar± SD	5.9 ± 2.3	7.40 ± 1.72	8.4 for deletion 7.2 for UPD	7.6 ± 2.7
Mean five minute Apgar ± SD	7.8 ± 1.1	8.79 ± 1.67	9.5 for deletion 8.7 for UPD	9.2 ± 2

NA = not available