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Clinical evidence of intrauterine disturbance in Prader-Willi syndrome, a genetically imprinted neurodevelopmental disorder

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Abstract

Background: Imprinted genes are considered to play an important role in growth and early development but much of the research is based on animal studies.
Aim: This study reports clinical data from a French population concerning prenatal, perinatal and postnatal complications in Prader-Willi syndrome (PWS), a genetically imprinted neurodevelopmental disorder associated with growth retardation, intellectual impairment and obesity.
Study design: Data from family health records concerning prenatal, perinatal and postnatal complications were collected from 52 French people with the deletion form (DEL), and 34 French people with the maternal disomy form of PWS (UPD) and compared against national norms and between groups.
Results: Significant findings include: a history of miscarriage, high rate of polyhydramnios (12/34 UPD, 11/52 DEL), a high rate of induced labour, a high rate of Caesarian section (20/34 UPD, 26/52 DEL), small gestational age (10/34 UPD, 22/52 DEL), hypotonia (34/34 UPD, 49/52 DEL), and suckling deficit (25/34 UPD, 46/52 DEL). Significant differences between genetic subtypes include a higher rate of induced labour in UPD (27/34 UPD, 25/52 DEL), an increased risk of premature term in UPD (9/34 UPD vs. 4/52 DEL), raised maternal age in UPD (36.4 years vs. 29.3 years), low birth weight for newborns with a deletion form of PWS (girls 2.8 kg, boys 2.7 kg), a positive correlation between parental weight and offspring birth weight only for patients with UPD (UPD maternal: $r=0.62$, paternal: $r=0.51$).
Conclusion: The results indicate significant intrauterine disturbance in PWS, particularly in PWS due to UPD, but a more significant weight disturbance for PWS due to deletion.

1. Introduction

Prader-Willi syndrome (PWS) is a genetically determined neurodevelopmental disorder first identified by Prader, Labhart and Willi in 1956 [1]. The clinical criteria were

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refined in 1993 [2], and again in 2001 as a result of improved genetic diagnosis [3]. The phenotype varies according to age. The cardinal features include neonatal hypotonia and poor sucking (0 to 2 years), global developmental delay (2 to 6 years), hyperphagia and propensity to obesity (6 to 12 years), mild learning difficulties, hyperphagia, hypogonadism, and behaviour problems such as temper tantrums and obsessive compulsive symptoms (13 years through adulthood). There is a primary underlying metabolic disturbance involving growth hormone deficiency [4] which together with hyperphagia, due to the absence of normal satiety mechanisms [5], results in both short stature and obesity. Diabetes mellitus, cardiac problems, respiratory problems and sleep apnoea are frequent complications [6]. A characteristic facial appearance, small hands and feet, and abnormal menses in female adults are also well documented [7].

Incidence and prevalence estimates vary across countries [8]. This variation has been attributed to methodological issues. A prevalence of 1:15,000 is commonly reported but recent studies in the UK and Australia report an estimated birth incidence of around 1:25,000; and a prevalence of 1:52,000.

Although rare, PWS is of particular interest because it was one of the first disorders to be identified involving genomic imprinting [9], a phenomenon demonstrating that certain autosomes have regions in which genes are differentially expressed depending on the gender of the parent of origin. PWS is caused by an absence of expression of genes in the 15q11-13 region on the paternal chromosome, which are imprinted (not expressed) on the maternal chromosome. Angelman syndrome (AS), another neurodevelopmental disorder with a different phenotype, is caused by the absence of maternally expressed genes which are imprinted on the paternal chromosome in the same region [10]. Mutations in the UBE3A gene, have been identified in 20% of people with AS.

The absence of paternally expressed maternally imprinted genes in PWS can arise by four different mechanisms [11]. The most common mechanism is a chromosome 15q11-13 deletion which accounts for 70% of PWS. The size of the deletion has been further defined as Type I (larger) and type II (smaller) [12]. The second most common form which accounts for 20–25% of PWS is a maternal disomy (UPD) in which two copies of chromosome 15 of maternal origin, and no chromosome 15 of paternal origin are inherited. Both these forms occur sporadically. Imprinting errors [13] due to either a sporadic or inherited microdeletion in the imprinting centre occur in 3% of individuals with PWS, and can be transmitted. A paternal chromosome balanced translocation, accounts for less than 1% of PWS. The gene or genes for PWS remain to be identified but several candidate genes are proposed including ZNF127, MAGEL2, NDN, IPW, SNURF-SNRPN, and snoRNAs [14–19].

Phenotypic differences between genotypes have been reported. For example in UPD, superior verbal intelligence [20], autism [21], and a greater risk of psychosis [22,23] have all been described. In deletion PWS, superior jigsaw puzzle skills [24] and greater severity of skin-picking [25] have been reported. Recent research has focussed on the impact of deletion size on phenotype but results are not consistent. Some studies report that a smaller deletion may result in fewer or less severe symptoms [26,27], whereas others show no significant differences [27,29]. It has also been suggested that there is a milder phenotype in females with UPD compared to deletions [30].

Concerning the neonatal phenotype, relatively few studies have been reported, and the results of these are inconsistent or contradictory. Hence a study of American neonates found that PWS due to UPD had a significantly lower birth weight than those with a deletion [31], whereas the converse was found in a study of German PWS babies [32]. A study of Brazilian neonates found that although there is a trend for those with UPD to be of lower weight, there was no statistically significant difference between genetic subtypes [29]. Shorter birth length has been documented in general for PWS babies [31] but only for UPD in the other studies [32]. One possible explanation for these variations is the influence of maternal body composition, which has been shown to have a significant influence on neonatal birth weight in the normal population [33]. Another potential confounding factor is the inclusion of premature babies, which may bias the results in a downward direction. Even using centiles for gestational age, it is not clear whether foetuses with PWS develop at the same rate compared to normal babies, and across genetic subtypes.

The pathophysiological basis of PWS remains unknown. One theory suggests that much of the PWS phenotype can be accounted for by the absence of expression of a maternally imprinted gene at 15q11-13 leading to an abnormality in one of the feeding pathways of the hypothalamus [34]. This model does not however account for the observed intellectual deficit in PWS and it has been proposed that the PWS genotype may also have effects on placental function and through this on early brain development. This hypothesis is based on the observation from animal studies that imprinted genes are highly expressed in the placenta and that the creation of embryos, whose genetic material is either completely of maternal or completely of paternal origin, has a marked effect on foetal growth and development [35].

Recent data from animal studies lends support to the presence of a foetal developmental abnormality in PWS [36]. Data concerning foetal development in humans with PWS, however, is lacking due to the sporadic incidence of the disorder, and non-detection of PWS during pregnancy.

The aims of the present study were first, to examine clinical evidence for disturbance of foetal growth and development in all human PWS genetic subtypes compared to the normal population; and second, to compare clinical features of the prenatal and neonatal stage of development between deletion and UPD genotypes. It is the first community study to be undertaken of the PWS population in France.

2. Method

2.1. Subjects

One hundred and four families throughout France with a child or adult with a confirmed genetic diagnosis of PWS were recruited through the French Prader Willi Association, a voluntary organisation. Included in the analysis were 25 females, and 27 males with a deletion subtype; and 19 females and 15 males with UPD, aged between 1 and 49. All already have had a genetic diagnosis from the medical genetic service either in the hospital where the child was born, or later in their locality. The protocol in France involves the diagnosis of PWS by DNA methylation test, fluorescence in situ hybridization (FISH) to detect a deletion; probes showing