Change in Prevalence of Congenital Defects in Children With Prader-Willi Syndrome

WHAT'S KNOWN ON THIS SUBJECT: The Prader-Willi phenotype is widely discussed in the literature. However, the prevalence of specific congenital defects in children with Prader-Willi syndrome is not well-described.

WHAT THIS STUDY ADDS: This study presents epidemiological data from children with Prader-Willi syndrome and demonstrates that these children have a significantly increased risk of having certain congenital defects. The presence of defects is independent of the etiologic subtypes.

abstract

OBJECTIVE: The aim of this study was to assess the prevalence of congenital defects observed in patients with Prader-Willi syndrome (PWS) and to compare this prevalence with that described in the general population. In addition, these findings were correlated with the different etiologic subtypes.

METHODS: A total of 180 children with PWS followed for 13 years were included in this study. Diagnosis was confirmed by the methylation test, and genetic subtypes were established by using fluorescence in situ hybridization or multiplex ligation-dependent probe amplification and microsatellite analyses. The prevalence of congenital defects was compared with national and international registries of congenital defects in the general population (Estudio Colaborativo Latinoamericano de Malformaciones Congénitas, European Surveillance of Congenital Anomalies, and the New York Registry).

RESULTS: Twenty-two percent of the patients presented congenital defects with a risk of 5.4 to 18.7 times higher than that of the general population. The most frequent congenital defects were heart defects, renal ureteral malformations, vertebral anomalies, hip dysplasia, clubfoot, and agenesis/hypoplasia of the corpus callosum. Each of these congenital defects was significantly more frequent in the children with PWS than in the general population. The congenital heart defects were more frequent in girls than in boys with PWS. No significant differences were found when the defects were correlated with the different etiologic subtypes.

CONCLUSIONS: An increased prevalence of congenital defects was found in our PWS patients. This finding suggests the need for further studies in PWS children that allow physicians to detect the congenital defects found in this series and, thus, to anticipate complications, with the ultimate aim of enhancing the management of PWS patients.

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KEY WORDS
Prader-Willi Syndrome, congenital defects in PWS, correlation with etiologic subtypes

ABBREVIATIONS
CDH—congenital dislocation of the hip
ECLAMC—Estudio Colaborativo Latinoamericano de Malformaciones Congénitas
EUROCAT—European Surveillance of Congenital Anomalies
PWS—Prader-Willi syndrome

Dr Torrado conceptualized and designed the study, coordinated and supervised data collection, analyzed and interpreted the data, and drafted the initial manuscript, and also reviewed and approved the final manuscript as submitted; Dr Foncuberta contributed to data collection, performed statistical analysis and interpreted the data, carried out MLPA analysis, and critically reviewed the manuscript and approved the final manuscript as submitted; Dr de Castro Perez designed the data collection instruments, and coordinated and supervised data collection, revised the manuscript and approved the final manuscript as submitted; Dr Gravina contributed to data collection, critically revised the manuscript and approved the final manuscript as submitted; Dr Araoz performed microsatellites analysis, carried out the initial data analysis, reviewed the manuscript, and approved the final manuscript as submitted; Dr Baialardo performed cytogenetic analysis, contributed to acquisition of data, reviewed the manuscript, and approved the final manuscript as submitted; and Dr Chertkoff substantially contributed to the study design, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Prader-Willi syndrome (PWS) is a complex multisystemic disorder. The clinical features of this syndrome have been widely described. Patients with PWS show severe pre- and postnatal hypotonia, feeding difficulties in the neonatal period, characteristic facial features, hypogonadism, intellectual disabilities, behavioral problems, excessive eating, and gradual development of morbid obesity. The clinical diagnostic criteria for PWS were developed through a consensus process in 1993. These criteria are an excellent guide for the recognition of the features that may be present in patients with this disease. PWS is present in all races, and is 1 of the most common diseases seen in genetics departments in different health care centers. The estimated prevalence of this syndrome varies from 1/10,000 to 1/25,000. 

PWS is caused by the loss of expression of the paternally inherited genes from chromosome 15q11-q13. This region contains imprinted sequences that are differentially expressed depending on the parent of origin. The lack of expression of the paternal genes occurs by 3 primary mechanisms: (1) deletion of a 5 to 6 Mb region on the paternally contributed chromosome, accounting for ~70% of the cases; (2) maternal uniparental disomy (m-UPD) found in ~25% of the patients; and (3) imprinting defects found in 2% of affected individuals. In addition, the deletions can be classified into 2 groups: type 1 and type 2, according to the breakpoints involved. These different mechanisms involved in PWS etiology are likely to produce differences in gene expression owing to the haploinsufficiency of genes in the region, partial gene expression, silencing differences, and a dosage effect of maternal genes in the cases of m-UPD, which might explain variations in the phenotype depending on the etiology. Several correlation studies between genotypic variants and different phenotypic manifestations have been performed since 1991. 

The current study included a large group of children with PWS, who were diagnosed and followed for 13 years by the same interdiscipli nary team. It was observed that many of the children presented congenital defects, not commonly described in this disease. To our knowledge, there are few reports describing the prevalence of congenital defects in PWS. The aim of the current study was to investigate the prevalence of congenital defects observed in PWS patients and to compare this prevalence with that described in the general population. Furthermore, these findings were correlated with the gender of the patient and the different etiologic subtypes of PWS. 

**METHODS**

This was a retrospective cohort study. A total of 195 children with PWS were followed at the Genetics and Pediatrics Departments of the Hospital de Pediatria “Prof. Dr. Juan P. Garrahan” (Buenos Aires, Argentina) from April 1998 to April 2011. Fifteen children were excluded owing to different causes: 4 had other chromosome aberrations and 11 did not attend the clinical controls with the established periodicity. Finally, 180 PWS children (87 girls and 93 boys) were included in the current study.

Clinical diagnosis was confirmed by the methylation test. To establish the etiology, fluorescence in situ hybridization (Vysis Inc, 2004) and microsatellite analyses were performed. In the past 3 years, fluorescence in situ hybridization analysis was replaced by multiplex ligation-dependent probe amplification (SALSA MLPA kit ME028/MRC-Holland). High-resolution cytogenetic analysis from peripheral blood leukocytes was performed according to a modified method by Yunis et al to rule out other chromosomal abnormalities. All children met the Holm clinical criteria according to age. The median age at diagnosis was 1.2 years (range, 0.01–17.25). Children <3 years of age or with severe comorbidities were clinically evaluated twice a year, whereas patients >3 years of age were followed annually.

Different complementary studies were requested from patients who showed positive signs of having other congenital defects. These included imaging studies: renal, abdominal, pelvic, vesical, cerebral, hip, and soft tissue ultrasound; spine, hip, and foot x-ray; tumor Doppler ultrasound and nuclear magnetic resonance of the spine and brain; ophthalmologic evaluation; and a biopsy of the bowel in the case of a child who had Hirschsprung disease.

**Database**

The following population registries were considered to compare the prevalence of birth defects: ECLAMC (Estudio Colaborativo Latinoamericano de Malformaciones Congénitas) 2010, corresponding to 7 geographic regions of Argentina; ECLAMC 2011 corresponding to 100 maternity units in South America; The Congenital Malformation Registry of New York State Department of Health; and the European Surveillance of Congenital Anomalies (EUROCAT) registries.

**Statistics**

The Fisher exact test was used. Odds ratios with 95% confidence interval were calculated for all and each congenital defect by using StatXact 3.1.

**RESULTS**

Different congenital defects were found in 40 PWS patients. None of them presented >1 birth defect (Table 1). Cardiac anomalies were the most common defects reported (4.4%): atrial septal defect (5 patients), atrial septal defect...
TABLE 1 Congenital Defects in PWS Patients

<table>
<thead>
<tr>
<th>Congenital Defects</th>
<th>No. of Cases</th>
<th>Gender</th>
<th>Age Detection, months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Renoureteral malformations</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Agenesis/hypoplasia of the corpus callosum</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Clubfoot</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Congenital hip dislocation</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Vertebral anomalies</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cataract</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hirschsprung</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gervicotorto lumbar syringomyelia</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anorchia</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular anomalies</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>25</td>
<td>17</td>
</tr>
</tbody>
</table>

and ductus (1 patient), ventricular septal defect (1 patient), and pulmonary stenosis (1 patient). Different renoureteral malformations were present in 5 patients (2.8%). Left renal hypoplasia, bilateral ureteral duplication, left bifid renal pelvis and vesicoureteral reflux, left pelvicalyceal dilation, and bilateral vesicoureteral reflux due to ureteral valves. Five patients (2.8%) had abnormalities of the corpus callosum, 1 with agenesis and 4 with hypoplasia. Clubfoot was observed in 2.8% of the patients, and congenital dislocation of the hip (CDH) in 3.33%. Vertebral anomalies were found in 2.8% of children: hemivertebrae (3 patients), vertebral fusion (1 patient), and rachischisis of 2 vertebrae (1 patient). Vascular anomalies were observed in 2 patients (1.11%); these consisted of large cavernous hemangiomas located on the thorax and neck, one of them required early surgical intervention.

Seventy percent (28/40) of the congenital birth defects described in this study were detected in the first 4 weeks of life. Only 7 birth defects (17.5%) were identified subsequent to the diagnosis of PWS: 1 renoureteral malformation, 2 hypoplasia of the corpus callosum, 2 vertebral anomalies, and the syringomyelia and anorchia found in this series.

The prevalence of congenital defects found in this PWS series (22.2%) was compared with the prevalence reported in 4 different registries in the general population (Table 2). The children with PWS studied had 5.4 to 18.7 times more risk of a congenital defect than the individuals in the general population.

The etiologic characterization of 180 patients considered in this study revealed that 109 presented a deletion, 68 a m-UPD and 3 an imprinting defect. To correlate the presence of birth defects with the different etiologic subtypes, the patients were classified into 2 groups: deleted \((n = 109)\) and nondeleted \((n = 71)\). No significant differences were found between the etiologic subtypes for any of the congenital defects studied (Table 3).

The presence of congenital birth defects was compared between both genders. Among the most frequent congenital birth defects observed in this population, the congenital heart defects were more frequent in girls \((P = .030)\). This finding differs from those described in the general population, in which no significant differences between both genders have been found.25,24

**DISCUSSION**

The current study assessed the prevalence of congenital defects in a population of 180 children with PWS. Based on the general population registries consulted, the prevalence of these defects was significantly higher than expected.

Some birth defects, such as cardiac anomalies, renoureteral malformation, clubfoot and CDH, which are frequently present in the general population, were also frequent in this PWS series, but their prevalence was significantly higher. Although, in the national and international registries consulted, there were no data reporting the prevalence of congenital vascular anomalies or vertebral malformations, 7 of the patients studied presented these defects. If these patients were excluded from the total number of congenital defects, the prevalence of birth defects in the PWS patients would still be significantly higher than the prevalence in the general population.

Agenesis/hypoplasia of the corpus callosum was found in 2.8% of the PWS patients studied. The prevalence found was significantly higher than that described in the registry of New York State, the only one that systematically records this anomaly. Other studies have already described different abnormalities of the central nervous system in patients with PWS by neuroimaging techniques.25–29 The presence of hypoplasia of the corpus callosum and severe cerebellar defects was only described by Titomantio et al29 in 1 PWS patient. Furthermore, Yamada et al27 found functional anomalies in PWS patients, which could indicate developmental abnormalities in the splenium of the corpus callosum.

Concerning multifactorial etiology of CDH and clubfoot, environmental factors appear to play an essential role in this group of children. The extreme pre- and postnatal hypotonia, usually present in PWS newborns, could be an important predisposing factor for the development of both defects. In line with this, Siapkara and Duncan30 described a high occurrence of equinovarus foot...
In children with neuromuscular diseases that present hypotonia. In addition, 50% of the children with CDH in our series had been delivered by podalic version, which could be related to the scarce intrauterine movement secondary to prenatal hypotonia. Delivery by podalic version is considered a predisposing factor for the development of CDH. There are few reports on hip dysplasia and equinovarus foot in patients with PWS. West and Bullock conducted an interesting study in which they ruled out obesity as a responsible factor for hip dysplasia, because they did not find slipped capital femoral epiphysis. The authors suggested hypotonia combined with ligament laxity as one of the mechanisms for the development of this type of dysplasia.

With regard to the correlation between the presence of birth defects and the different etiologic subtypes, we expected to find a higher frequency in the group of patients with deletion due to the loss of several genes. However, no significant differences were found between the etiologic subtypes. It would be interesting to perform comparative genomewide microarrays and other genomic approaches to interrogate genome regions that may be associated with the higher prevalence of congenital anomalies in this population. In the current study, 90% of the birth defects were detected within the first 2 years of life, a period similar to that considered in the New York and EUROCAT registries. Furthermore, 82.5% of all the defects were detected before the diagnosis of PWS. Thus, the highest risk of congenital malformations in this group of children could not be attributed to a follow-up bias.

Finally, the findings described in this study can be applied in pediatric clinics. PWS is a multisystemic and complex disease. Knowing that there are no registries were found for vertebral and vascular malformations.

### TABLE 2: Prevalence of Congenital Defects in PWS and General Population

<table>
<thead>
<tr>
<th>Congenital Defects</th>
<th>PWS (n = 180)</th>
<th>ECLAMC 2010 (n = 855 220)</th>
<th>ECLAMC 2011 (n = 18 491)</th>
<th>EUROCAT (n = 3 638 216)</th>
<th>New York (n = 242 364)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate</td>
<td>No. of Cases</td>
<td>Rate</td>
<td>Fisher Exact Test</td>
</tr>
<tr>
<td>Total congenital defects</td>
<td>40</td>
<td>2222.2</td>
<td>12 846</td>
<td>150.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>8</td>
<td>444.4</td>
<td>1711</td>
<td>20.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urogenital malformations</td>
<td>5</td>
<td>277.8</td>
<td>914</td>
<td>10.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Agenesis/hypoplasia of the corpus callosum</td>
<td>5</td>
<td>277.8</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clubfoot</td>
<td>5</td>
<td>277.8</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Congenital hip dislocation</td>
<td>6</td>
<td>333.2</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CI, confidence interval; NA, data not available; OR, odds ratio. —, indicate data not calculated because the number of cases is not available.

- Cataracts, Hirschsprung, syringomyelia, and anorchia are not included in this table because each of these defects was found only once in different patients. No registries were found for vertebral and vascular malformations.
- Cases per 10,000.
- Includes all defects listed in Table 1.
associated congenital anomalies such as cardiopathies or renoureteral defects may allow physicians to perform a specific and timely treatment to avoid unexpected complications in the usual clinical management of the disease. The early detection of a spinal malformation in patients who often have scoliosis may lead to a better definition of appropriate strategies for orthopedic management. On the other hand, this knowledge can help avoid underestimating the diagnosis of PWS in hypotonic infants that have other anomalies such as agenesis of the corpus callosum or heart defects.

The findings of this study strongly suggest the need to include new studies that complement the integral evaluation recommended for the follow-up of patients with PWS. In this respect, we suggest that all children with PWS should undergo a series of studies at the time of diagnosis that are noninvasive and low cost: abdominal, renal, and hip ultrasound, cardiologic evaluation, spine x-ray, and at least 1 cerebral ultrasound, if the patient is an infant. We recommend including these studies in the anticipatory guidelines for the care of patients with PWS, which would allow physicians to perform an adequate and personalized management of each patient.

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