Harmonize

Williams Syndrome in Europe

Rome, 17th October 2015

Rare clinical features in Williams Syndrome

Dr. M.Cristina Digilio

Medical Genetics, Bambino Gesù Hospital, Rome
Characteristic clinical features of WS

- Facial anomalies
- Developmental delay
- Congenital heart defect
- Hypertension
- Hernia
- Strabismus
### Frequency of clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial anomalies</td>
<td>100%</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>97%</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>75-80%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20%</td>
</tr>
<tr>
<td>Strabismus</td>
<td>50%</td>
</tr>
<tr>
<td>Hernia</td>
<td>40%</td>
</tr>
</tbody>
</table>
The clinical expression of the syndrome is wide, and rare clinical features can be misdiagnosed.

The knowledge of the possible association between feature and syndrome is an important marker for clinicians in the diagnostic approach and clinical management.
Rare clinical features in Williams Syndrome

- Supravalvular aortic stenosis
- Peripheral stenosis of the pulmonary arteries
Rare clinical signs in the rare Williams Syndrome

Identification and characterization of seven novel mutations of elastin gene in a cohort of patients affected by supravalvular aortic stenosis

Lucia Micale1, Maria Giuseppina Turturo, Carmela Fusco, Bartolomeo Augello, Luis A Perez Jurado, Claudia Izzi, Maria Cristina Digilio, Donatella Milani, Elisabetta Lapi, Leopoldo Zelante and Giuseppe Merla

Rare clinical features in Williams Syndrome

Description of the cardiac defects in the 113 patients with Williams-Beuren syndrome.

<table>
<thead>
<tr>
<th>Defect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supravalvar aortic stenosis</td>
<td>73 (64.6%)</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>51 (45.1%); isolated in 18 (15.9%)</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>9 (7.9%); isolated in 4 (3.5%)</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>7 (6.2%); isolated in 3 (2.6%)</td>
</tr>
<tr>
<td>Mitral valvar prolapse</td>
<td>7 (6.2%); isolated in 3 (2.6%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>4 (3.5%); isolated in 1 (0.9%)</td>
</tr>
<tr>
<td>Aortic insufficiency</td>
<td>1 (0.9%); associated with supravalvar aortic stenosis</td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>1 (0.9%); associated with pulmonary stenosis</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>2 (1.8%); associated with mitral valvar prolapse and pulmonary stenosis</td>
</tr>
</tbody>
</table>

• High prevalence of atypical cardiac defects, found in almost one-fifth, and particularly the frequency of ventricular septal defects, present in just over onetwentieth of our total population.

New Findings concerning Cardiovascular Manifestations emerging from Long-term Follow-up of 150 patients with the Williams-Beuren-Beuren syndrome

Alessia Del Pasqua, Gabriele Rinelli, Alessandra Toscano, Roberta Iacobelli, Cristina Digilio, Bruno Marino, Claudia Saffirio, Sergio Mondillo, Luciano Pasquini, Stephen Pruett Sanders, Andrea de Zorzi

Cardiology in the Young (2009), 19, 563–567
This prevalence of VSD is higher than in the general population, and could be explained by better detection in syndromic patients undergoing a detailed cardiac evaluation.

The role of contiguous genes within the critical region has not been defined, and could contribute to development of these atypical defects.

New Findings concerning Cardiovascular Manifestations emerging from Long-term Follow-up of 150 patients with the Williams-Beuren-Beuren syndrome
Alessia Del Pasqua, Gabriele Rinelli, Alessandra Toscano, Roberta Iacobelli, Cristina Digilio, Bruno Marino, Claudia Saffirio, Sergio Mondillo, Luciano Pasquini, Stephen Pruett Sanders, Andrea de Zorzi
Cardiology in the Young (2009), 19, 563–567
The vascular involvement in sites different from the aorta can be etiologically linked to the elastin defect.

**OCULAR**

Diffuse arterio-venous tortuosity (27%)  
Weber et al., 2014

**ABDOMINAL**

Iuxtarenal abdominal aorta coarctation  
Celiac artery stenosis  
Superior mesenteric artery stenosis  
Roux et al., 2012

**CORONARY**

Multiple-site coronary artery re-stenosis and aneurisms  
Serena et al., 2015
Rare clinical signs in the rare Williams Syndrome

- Characteristics of peripheral vascularity, coronary arteries, and cerebral vessels of patients with WS may specifically complicate both history or treatment procedures, such as cardiac catheterization, anesthesia, and surgery.

- Due to the frequent association with coronary artery stenosis, the preoperative assessment must include coronary angiography.

- Specific perioperative procedures are needed in order to minimize the risk factors associated with this syndrome including difficult intubation and/or ventilation and/or intubation and atypical reaction to drugs, and temperature regulation.

Genetic syndromes and congenital heart defects: how is surgical management affected?

Roberto Formigari, Guido Michielon, Maria Cristina Digilio, Gerardo Piacentini, Adriano Carotti, Alessandro Giardini, Roberto M. Di Donato, Bruno Marino.

In patients with WS who are admitted to a hospital with complaints of failure to thrive and vomiting, cricopharyngeal achalasia should be kept in mind in the differential diagnosis by clinicians. The main reasons for oropharyngeal dysphagia in children are the incomplete relaxation, premature closure, or delayed relaxation of the upper esophageal sphincter, epiglottic dysfunction, or paresis of pharyngeal constrictor muscles. Cricopharyngeal dysfunction can be primarily associated with upper esophageal sphincter motility disorder or the central nervous system disorders. Although the accurate treatment, achalasia may occur again because of underlying elastin gene defect in WS. At that point, control imaging is significant in planning possible repetitive therapeutic procedures. The clinicians should be aware that early diagnosis, timely treatment, and follow up of the patients are very important in WS to prevent preoperative and postoperative complications.

**Cricopharyngeal achalasia**

Recurrent Cricopharyngeal Achalasia in a Child With Williams–Beuren Syndrome
Tu˘may Bekçi, Meltem C. Bilgici, Eser Turgut, Burak Tander
The Journal of Craniofacial Surgery 2015
The prevalence of CD in the series of WS patients by Giannotti et al. was 9.5% (6/63), compared to 0.54% (1/184) in the Italian students (p<0.001).

A less severe form of CD is found in some patients with WS and CD, as in some subjects with distinct chromosome disorders.

Failure to thrive was a constant feature in these CD patients, while anorexia and diarrhoea occurred in half of them.

Coeliac disease in Williams syndrome
Aldo Giannotti, Giovanni Tiberio, Massimo Castro, Fabio Virgilii, Franco Colistro,
Francesca Ferretti, Maria Cristina Digilio, Manuela Gambarara, Bruno Dallapiccola
Hypercalcaemia was previously considered a characteristic symptom of WS.

Probably due to the changing in feeding and types of milk which are used, the reviews in the letter series of patients with WS are showing that this feature is becoming rare.
None of our patients had overt hypothyroidism;

29 patients (31.5%) had subclinical hypothyroidism.

Thyroid antibodies were absent in all patients.

The prevalence of patients with subclinical hypothyroidism was significantly higher in the younger patients.

Ultrasonography revealed morphological or volumetric abnormalities of the thyroid gland in 67.5% of patients; these abnormalities were more frequently observed in the older children.

Thyroid Morphology and Subclinical Hypothyroidism in Children and Adolescents with Williams Syndrome
PAOLA CAMBIASO, MD, CINZIA ORAZI, MD, MARIA CRISTINA DIGILIO, MD, SANDRO LOCHE, MD, ROSSELLA CAPOLINO, MD, ALBERTO TOZZI, MD, ANTONELLA FAEDDA, PHD, AND MARCO CAPPA, MD
Epilepsy is considered to be a rare symptom in WS.

Among the genes deleted distally to the WS common deletion interval, HIP1 and YWHAG have been proposed as the most compelling candidate genes for susceptibility to autistic traits, epilepsy, and ID.
Three out of four of the eWBS patients in this series carried typical WBSCR, and no deletion included HIP1, YWHAG or MAGI2.

Epilepsy is a Possible Feature in Williams-Beuren Syndrome Patients Harboring Typical Deletions of the 7q11.23 Critical Region
Francesco Nicita, Giacomo Garone, Alberto Spalice, Salvatore Savasta, Pasquale Striano, Chiara Pantaleoni, Maria Valentina Sparta, Gerhard Kluger, Giuseppe Capovilla, Dario Pruna, Elena Freri, Stefano D’Arrigo, and Alberto Verrotti
Rare clinical signs in the rare Williams Syndrome

Peculiar familial occurrences of different diseases can be evidenceable in some families.

Molecular studies are needed in order to verify genetic predisposition of some couples to different diseases.

Rare Genomic Rearrangement in a Boy With Williams–Beuren Syndrome Associated to XYY Syndrome and Intriguing Behavior


Rare clinical signs in the rare Williams Syndrome

Peculiar familial occurrences of different diseases can be evidenceable in some families

Co-occurrence of a de novo Williams and 22q11.2 microdeletion syndromes

Shukl et al., Am j Med Genet 2015
Peculiar familial occurrences of different diseases can be evidenceable in some families.

Co-occurrence of deletion 7q11.23 – Williams syndrome and heterozygous change in MLL2 – Kabuki gene in a patient with peculiar facial anomalies and cardiac defect (double outlet right ventricle)

Consider multiple defects in patients with atypical features
Main Partners:

AISW Onlus
C/o Sovrano Militare Ordine di Malta Delegazione di Roma
Grillo Place, No.1
00184 Rome
Telephone: (+39) 06 65596357
Fax: (+39) 06 45440763

E-mail: hwsie@aisw.it
Web site: www.hwsie.aisw.it